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IN FENNIA: Erik Adlercreutz, Woldemar Backman, Bertel von Bonsdorff, Mons-Christian Ehrström, Erik Hisinger-Jägerskiöld, Martin Savolin, Pauli Soisalo, J. Wahlberg, E. A. v. Willebrand.

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(From Bispebjerg Hospital, Copenhagen, Medical Departments B and C,  
Chiefs: Prof. E. Meulengracht and Prof. K. Secher.)

## Response of blood prothrombin to vitamin K as a measure of hepatic function.

By

P. FROM HANSEN and HOLGER BEGTRUP.<sup>1</sup>

(Submitted for publication September 2, 1942).

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The prothrombin level in the blood is often lowered in jaundice, both in that of obstructive and in that of parenchymatous origin; the low level may probably result from different mechanisms and the problem arises: Is the low level of prothrombin in either case simply due to an inhibited absorption of vitamin K on account of decreased excretion of bile acids, i. e. a K-avitaminosis in the strict sense, or *is the prothrombin-forming power of the liver also impaired in parenchymatous jaundice?*

During later years numerous cases of jaundice with low prothrombin levels in the blood have been published. Following administration of vitamin K the prothrombin level rose to normal in several patients, whilst in other cases the rise was very small or nihil.

The idea of measuring the hepatic function by the rise in blood prothrombin following the administration of vitamin K has been put forward by Tage-Hansen (14), Thordarson (15), and others, but none of these authors have suggested a method for a test.

After the present work had been started in February 1941, Koller (8), Hult (7) and Lord & Andrus (10) have published inves-

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<sup>1</sup> Presented in »Dansk Selskab for Intern Medicin» 27.—2.—1942.

tigations which in different ways give a test of hepatic function as an aid for the differential diagnosis.

The doses of vitamin K used by Koller and by Hult — 30 and 10 mgs respectively — are (at any rate in cases of slight hepatic damage) far above the minimum required to raise the blood prothrombin level to normal. Neither do these authors take the prothrombin level prior to administration of vitamin K into account — they simply determine whether the level becomes normal or not, and do not consider the absolute rise in prothrombin concentration. According to the present authors the latter point is absolutely essential.

By the above method, therefore, a certain diagnosis cannot be made if the prothrombin level reaches the normal, i. e. after Koller and after Hult the diagnosis obstructive jaundice cannot be made with certainty.

Lord & Andrus, however, consider the absolute rise in prothrombin level, and they are therefore also able to distinguish between parenchymatous and obstructive jaundice even if the prothrombin level does not reach the normal. They administer only 2 mgs menadione, which preparation, however, measured in Dam units (5), is nearly twice as strong as the «Kvitasol» which was used in the present experiments. Menadione, which is dissolved in oil, is administered intramuscularly. If the prothrombin level has risen more than 10 per cent. during 24 hours, jaundice should be due to obstruction. If the prothrombin level has not risen 10 per cent., the determination is repeated 24 and 72 hours after the administration; if during the latter period the rise is not 15 per cent. in all, jaundice is intrahepatic in origin, whilst a rise of more than 15 per cent. speaks strongly in favour of obstruction. The fact that it may last more than 24 hours before the maximum rise is obtained is probably due to menadione being dissolved in oil; with preparations dissolved in water Koller (8) and others have found the maximum rise 24 hours after administration.

### Authors' Own Data.

The sensitivity of the liver to vitamin K can only be graded numerically if the vitamin is administered in doses so small that the prothrombin level is not brought to normal; the sensitivity is

expressed by the rise in prothrombin level per weight unit vitamin K administered. If the dose administered is so large that the prothrombin level rises to normal, the estimated sensitivity may be too low, as the effect of the possible excess of vitamin K cannot be included in the calculation.

We have therefore examined the sensitivity of the liver to such small doses, and have attempted to decide whether there is a significant difference in sensitivity between obstructive and parenchymatous jaundice.

In accordance with the above, we have introduced the concept »vitamin K sensitivity» — in abbreviation »KS», which covers the percentage rise in the blood prothrombin level during 24 hours per 2 mgs 2-methyl, 1, 4-naphthohydroquinonedisuccinate administered.

The dose has been set at 2 mgs; larger doses may often — particularly in obstruction — cause a rise to normal values.

In the majority of our cases KS has been determined after the administration of 2 mgs Kvitasol<sup>1</sup>. In several cases the dose exceeded 2 mgs, and in the latter cases we have, when we found it was justifiable, calculated the KS by simple division; such a calculation seems permissible.

Prothrombin was in the majority of the cases determined by the method of Hjalmar Larsen and Plum (9) for venous blood. The percentages have been read from the characteristic given by these authors. In a few cases the method of Dam and Glavind (6) or of Plum and Dam (12) was used.

### Vitamin K sensitivity in obstruction and in parenchymatous jaundice.

The tables show that in the cases where it was possible to calculate KS it was between 31 and  $\geq 53$  in obstruction, whilst in parenchymatous cases the values were between 0 and 11; 50 per cent. of the latter values were below 1.

We wished to see whether the above great difference between hepatic sensitivity to vitamin K in obstruction and in parenchymatous affections could be verified from cases previously published by other authors. We went through the published cases of definite

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<sup>1</sup> This preparation was kindly placed at our disposal by »Loven Chemical Works», Denmark.

obstruction and parenchymatous jaundice which had been treated with vitamin K and in which the prothrombin level had been determined (1, 2, 7, 8, 11, 13). When the figures allowed, we determined the sensitivity to vitamin K. In 7 publications we found 98 patients in all suitable for our present object. 55 cases were of obstruction and they all showed a pronounced response to vitamin K; 43 cases were parenchymatous affections, and their response was but slight. (As mentioned above only 3 of the authors (7, 8, 10) have attempted to use the response to vitamin K as a diagnostic measure). The cases with obstruction which had been treated with doses of vitamin K so large that a calculation of sensitivity was illusionary, were omitted

#### A. Cases with obstruction of the bile ducts.

Table I.

Patients with obstructive jaundice. In cases 1, 2, 3 and 7 the diagnosis was verified post-mortem, and in cases 4, 5 and 6 at operation.

| Nr | Diagnosis:                               | Prothrombin<br>level in per cent<br>before after | Rise in<br>prothrombin-<br>level | Dosage of<br>Vitamin K<br>in mg             | «KS»                   |
|----|--|--|----------------------------------|---|------------------------|
| 1  | Cancer pap. Vateri                       | 66 normal<br>66 normal                           | $\geq 34$<br>$\geq 34$           | 160 pr. os.<br>60 i. v.                     |                        |
| 2  | Cancer pap. Vateri.                      | 5 normal<br>(in the course of<br>6 days)         | $\geq 95$                        | 370 pr. os.<br>(in the course<br>of 6 days) |                        |
| 3  | Cancer pap. Vateri.                      | 31 normal  | $\geq 69$                        | 20 i. v.                                    |                        |
| 4  | Tumor pancreatis.                        | 37 normal<br>52 normal                           | $\geq 63$<br>$\geq 48$           | 4 pr. os.<br>2 i. v.                        | $\geq 31$<br>$\geq 48$ |
| 5  | Cholelithiasis.                          | 25 normal  | $\geq 75$                        | 60 i. v.                                    |                        |
| 6  | Cholecystitis et<br>Pericholecyst.chr.   | 38 83  | 45                               | 2 pr. os.                                   | 45                     |
| 7  | Cancer pap. Vateri<br>c. metast. ad hep. | 47 normal  | $\geq 53$                        | 2 pr. os.                                   | $\geq 53$              |

In cases 1, 2, 3 and 5 KS was not calculated, as the dose of vitamin K administered by far exceeded the dose which might just have caused a normal prothrombin level.

In all the remaining cases KS was found  $> 30$ .

*B. Cases with parenchymatous hepatic disease.*

Table II.

Patients with hepatitis and biliary cirrhosis. In cases 8, 9, and 10 the diagnosis was verified at operation with biopsy of hepatic tissue; in the remaining cases, which were all diagnosed as acute hepatitis, the course of the disease was typical and all cases recovered.

| Nr | Diagnosis   | Prothrombin level in per cent<br>before after |        | Rise in<br>Prothrombin<br>level | Dosage of<br>Vitamin K<br>in mg | •KS•     |
|----|---|---|--------|---------------------------------|---------------------------------|----------|
| 8  | Hepatitis chr. l. g.<br>(Cirrhosis) Lues<br>antea | 37  | normal | $\geq 63$                       | 40 i. v.                        | $\geq 3$ |
| 9  | Hepatitis chr.                                    | 60  | normal | $\geq 40$                       | 10 i. v.                        | $\geq 8$ |
|    |   | 60  | 70     | 10                              | 540 pr. os.                     | 1        |
|    |   | 52  | 80     | 28                              | 60 i. v.                        | 1        |
| 10 | Hepatitis chr.<br>(Cirrhosis incip.)              | 40  | 64     | 24                              | 80 i. v.                        | 1        |
|    |   | 44  | 68     | 24                              | 50 v. i.                        | 1        |
| 11 | Hepatitis ac. in<br>nosocom.                      | 66  | 69     | 3                               | 160 pr. os.                     | 1        |
| 12 | Hepatitis ac.                                     | 68  | normal | $\geq 32$                       | 10 pr. os.                      | $\geq 6$ |
| 13 | Hepatitis ac.                                     | 42  | 57     | 15                              | 30 pr. os.                      | 1        |
|    |   | 70  | 77     | 7                               | 10 pr. os.                      | 1 1/2    |
|    |   | 77  | 79     | 2                               | 50 i. v.                        | 1        |
| 14 | Hepatitis ac.                                     | 20  | 42     | 22                              | 10 pr. os.                      | 4        |
|    |   | 42  | 59     | 17                              | 50 i. v.                        | 1        |
| 15 | Hepatitis ac.                                     | 37  | 34     | $\div 3$                        | 2 pr. os.                       | < 0      |
|    |   | 33  | 40     | 7                               | 10 pr. os.                      | 1        |
|    |   | 39  | 59     | 20                              | 50 pr. os.                      | 1        |
| 16 | Hepatitis ac.                                     | 65  | normal | $\geq 35$                       | 10 pr. os.                      | $\geq 7$ |
|    |   | 60  | 67     | 7                               | 2 pr. os.                       | 7        |
|    |   | 60  | 69     | 9                               | 4 pr. os.                       | 5        |
|    |   | 77  | normal | $\geq 23$                       | 10 pr. os.                      | $\geq 5$ |
| 17 | Hepatitis ac. e<br>usu Salvarsan                  | 62  | 84     | 22                              | 4 pr. os.                       | 11       |
|    |   | 84  | normal | $\geq 16$                       | 10 pr. os.                      | $\geq 3$ |

In all these cases the value of KS was below 11, in most of them about 1 or below. In case 9 three determinations were made at intervals of 6 weeks, and the variations in KS corresponded to the clinical course of the disease and to the variations in the icteric index. In case 16 four determinations were made at intervals of one week; the clinical condition of the patient did not change during the first 3 weeks, whilst it improved during the fourth week.

(cf. cases 1, 2, 3, 5 of the present work). It is noteworthy that in all the published cases of obstruction the prothrombin level rose to normal values. In some cases which have been classified as obstruction the response to vitamin K was slight; in all these cases, however, the obstruction was due to cancer, and no information has been given regarding the condition of the liver, particularly it has not been stated whether metastases were found; the latter cases have therefore been omitted.

*C. Other cases with lowered prothrombin level.*

Table III.

In cases 18, 19, 20 and 21 the diagnosis was verified post-mortem, in case 23 by biopsy.

| Nr | Diagnosis                                     | Prothrombin level in per cent<br>before after |        | Rise in Prothrombin level | Dosage of Vitamin K in mg | «KS»            |
|----|---|---|--------|---------------------------|---------------------------|-----------------|
| 18 | Hyaloserositis (hep. lien., peric.)           | 66  | 58     | $\div 8$                  | 10 pr. os.                | $< 0$           |
| 19 | Cancer ventric. cum metast. ad hep. et ovarii | 5   | 60     | 55                        | 80 i. v.                  | $1 \frac{1}{2}$ |
| 20 | Cancer hep. (prim.?)                          | 50  | normal | $\geq 50$                 | 10 pr. os.                | $\geq 10$       |
| 21 | Abscessus hep. sine icterus.                  | 63  | normal | $\geq 37$                 | 2 i. v.                   | $\geq 37$       |
| 22 | Erythema nodosum                              | 23  | 34     | 11                        | 160 i. v.                 | 1               |
|    |   | 34  | 52     | 18                        | 60 i. v.                  | 1               |
|    |   | 52  | 40     | $\div 12$                 | 60 i. v.                  | $< 0$           |
|    |   | 40  | 48     | 8                         | 210 i. v.                 | 1               |
|    | half a year later                             | 100   |        |                           |                           |                 |
| 23 | Lymfogranulomatosis maligna sine icterus      | 75  | normal | $\geq 25$                 | 2 i. v.                   | $\geq 25$       |

### Discussion.

*Clinical importance of KS.* In four of our cases the differential diagnosis was before operation based alone on the KS. The details of these cases are:

Case 4: 4 months prior to operation the patient had developed jaundice, the intensity of which had varied somewhat, but it had on the whole increased gradually. After 3 months the liver was punctured and the histological picture was interpreted as subacute hepatitis. All the same the patient was operated upon because of the value of the KS, and an obstructing tumour was found in the pancreas with dilatation of the choledochus. The slightly damaged hepatic tissue was probably the result of the prolonged biliary stasis (3 months); the power of prothrombin formation had, however, not been impaired to any considerable degree.

In Case 6 the patient had for 3—4 years suffered from repeated attacks of pain, accompanied by jaundice. The x-ray showed numerous stones in the gall-bladder, but Bauer's galactose test showed an excretion of 2.6 grammes and the Takata-Ara test was ++ positive. KS, however, indicated obstruction; operation revealed a pronounced pericholecystitis and cholecystitis with a thickening of the walls which had probably caused obstruction.

Case 9: The patient had jaundice for a long period without other characteristic symptoms, wherefore it was not considered advisable to postpone operation, but nothing abnormal was found; histological examination of hepatic biopsy gave the diagnosis chronic hepatitis.

Case 10: The patient had for several years suffered from abdominal pain of no characteristic type; on admission she was jaundiced and again had an attack of pain. In spite of a KS below 1 the patient was operated upon; operation revealed nothing abnormal. Histological examination of hepatic tissue taken by biopsy showed an incipient cirrhosis.

As will be seen in the tables the values of the increase in prothrombin level or the KS are often larger than or equal to a certain value. This expression has been used in the cases that had received sufficient vitamin K to make their prothrombin level normal, i. e. the dose of vitamin K administered has been too large for the object in hand.

In their publications Koller and Hult have used the fact whether the prothrombin level became normal or not as a criterion for distinguishing between obstructive and parenchymatous jaundice. This criterion is hardly reliable, which may for instance be seen from case 16: The first and fourth determinations of KS were made after the administration of 10 and 10 mgs Kvitazol respectively, and the prothrombin level became normal. The second and the third determinations of KS followed administration of 2 and 4 mgs respectively; the prothrombin level became only subnormal and the values of KS were 7 and 5 respectively, which after the present method gives the diagnosis hepatitis.

*Limitations of the method.* KS can only be determined if the prothrombin level of the patient is below normal. In hepatitis this will usually occur in about only 50 per cent. of the cases — the present authors found a normal prothrombin level in the blood in 7 out of 18 cases. Other authors have stated corresponding figures (7, 8, 14). In complete obstruction hypoprothrombinaemia will at any rate develop after 2—3 weeks.

Evaluation of the method faces two ways: 1) With how much certainty are we able to prove an obstruction? 2) With how much certainty a parenchymatous affection?

1) Our data include no case of jaundice with obstruction with a KS below 31; there is, however, a patient with lymphogranulomatosis in whom KS was above or equal to 25, i. e. such a case might faultily lead to the diagnosis obstruction. 2) No case of jaundice of parenchymatous origin was found with a KS higher than 11. — Case 22 shows a cryptogenetic hypoprothrombinaemia, refractory to vitamin K (similar cases have been published by Bechgaard(3)). If such a patient should develop obstruction a possibility for a faulty diagnosis may be present.

Obstruction of long duration may easily cause impairment of the parenchyma, which should theoretically be able to lower the KS; in the cases 4, and 7, however, the KS was not low in spite of jaundice of 4 and 3 months standing respectively.

In two cases of cancer metastases to the liver, which — contrary to case 7 — had not been preceded by obstruction, the value of KS was  $1\frac{1}{2}$  (the prothrombin level rose from 5 to 60 following 80 mgs K) and  $\geq 10$  (from 50 per cent. to normal following 10 mgs K) respectively.



### Conclusion.

It seems that affections of the liver parenchyma are always accompanied by a KS below 20 (the slight impairment of the hepatic tissue which follows prolonged obstruction excepted) — but a KS of this low level is not pathognomic for parenchymatous affections, cf. case 22 and the above cases of cancer of the liver.

It seems that in pure obstruction KS is always above 20, but neither this is pathognomic, cf. case 23.

At present the authors are examining a large series of patients with jaundice. If further data verify the above findings, it looks as if an affection of the hepatic tissue may be definitely excluded if KS exceeds a certain value — as well as it will probably be possible to eliminate obstruction if KS is below a certain value. This limiting value will presumably be about 20.

The cause of the lowered prothrombin level may lie in a reduction of the hepatic power of prothrombin formation, or — and ? — in a reduction of the power of forming bile acids, followed by a reduced absorption of vitamin K. Only the reduction in power of prothrombin formation can influence the KS, whilst decrease in formation of bile acids would be of no effect. The fact that none of the above cases of parenchymatous affection have a normal KS may be explained by the hypothesis that the hepatic power of forming prothrombin is more vulnerable than the power of forming bile acids, so that an avitaminosis K in the strict sense does not occur in hepatitis; the avitaminosis due to impaired absorption, which in cases of parenchymatous affections may accompany the decreased power of prothrombin formation, is eliminated by the fact that the vitamin K administered is water-soluble.

### Summary.

The effect of vitamin K upon the prothrombin formation has been examined in 8 patients with obstructive affections of the hepatic ducts and in 10 patients with impairment of the liver parenchyma. The result was that a pronounced difference was found in the sensitivity of the two groups to vitamin K, a difference which could be verified by going through about 100 cases in literature. The above sensitivity has been numerically graded by calculating

the rise in the blood prothrombin level which follows the administration of 2 mgs 2-methyl, 1, 4-naphthohydroquinonedisuccinate (Kvitasol »Leo«). This rise is called the »vitamin K sensitivity» (»KS«), and in 4 determinations on obstructive cases it was found to be above 31, in 16 determinations on the cases of parenchymatous affections it was less than 11, in 50 per cent. of the latter even  $< 1$ . The diagnostic aid which may lie in the determination of KS is discussed.

For details see previously published work. (4)

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(From Blegdamshospitalet, Copenhagen. Chief: Professor H. G. A. Lassen,  
M. D.)

## **A Comparative Study of the Occurrence of Complications in Scarlet Fever Treated with Sulphanilamide, Specific Immune Serum and Normal Horse Serum, with a Reference to certain Clinical Features of the Material.**

By

**FRITS NEUKIRCH, VAGN ZAHLE & INGER BAUMGARTEN.**

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In 1935 Domagk (1) demonstrated the effect of prontosil in the case of infection with haemolytic streptococci in mice. Subsequent investigations [Trefouëls, Nitti and Bovet (1 a) and Buttle, Gray and Stephenson (2)] showed that in the organism prontosil splits off sulphanilamide and that in all probability the only active element is the freed sulphanilamide.

Since these results were published a large number of reports have been issued on the effects of sulphanilamide on infections in man caused by haemolytic streptococci.

The very good results achieved from the treatment of puerperal fever [Colebrook and Kenny (3)] and to some extent erysipelas [Snodgrass and Anderson (4)] led to sulphanilamide treatment being tried out in other diseases in which haemolytic streptococci were regarded as the etiological factor.

The etiology of scarlet fever has not yet been made clear in every detail, but the presence of haemolytic streptococci can be demonstrated in conjunction with all the purulent complications of that disease; furthermore, these bacteria can be cultivated from

the throats of practically all patients. Even if in the etiology of scarlet fever some importance may perhaps be attached to an ultra-visible virus in addition to haemolytic streptococci, it was reasonable to suppose that in scarlet fever sulphanilamide would have some effect, prophylactic at any rate, by perhaps preventing the appearance of complications. We do not yet know all the details of the action of sulphanilamide, but it is very probable that it consists of a direct action on the bacteria, manifested by a bacteriostatic effect or by a destruction of the microorganisms whereas the drug has no effect on the soluble toxin. Consequently it is natural to differentiate between the effect on the primary toxic phase of the disease and the preventive effect on the complications.

There is fairly complete agreement among investigators that sulphanilamide has no effect on the primary toxic phase, but there is marked disagreement with regard to its prevention of complications. One of the reasons for this disagreement is that the groups in the various works are not always directly comparable. What is more, there is a great difference in the frequency of the complications in the untreated groups. This frequency varies between 10 and 70 per cent. There are several explanations. In the first place, the complication frequency in the various epidemics may be very different; in the second place, there is variation in what individual authors consider to be complications, some of them reckoning adenitis and certain other manifestations as the usual symptoms of scarlet fever. Finally, the authors do not always differentiate between number of patients with complications and the total number of complications, and these two figures are sometimes very different. If the effect of sulphanilamide on the frequency of complication is to be appraised, we must see whether the total number of patients with complications is reduced, and what complications become fewer in number, as it must be particularly conclusive if sulphanilamide is capable of reducing the frequency of the more serious and protracted complications, first and foremost otitis.

To judge from the literature available the effect of sulphanilamide in preventing complications is doubtful. Some investigators [Hogarth (5), Peters and Havard (6), Sako, Dwan and Platou (7), Julius Strøm (8), Hamilton and Togasaki (9), le Fèvre (10)] con-

sider that it has an effect. Hogarth (5) has examined 350 cases, one-third of which were not treated, about a third received anti-scarlatina serum intramuscularly, and about a third were given serum and «proseptasine» (parabenzylaminobenzenesulphonamide). He himself states that there was no effect from this latter drug, but a close examination of the figures reveals a slight advantage to those treated with it; in the group «no treatment» 28.7 per cent. of the patients had complications, whereas in the serum group the percentage was 23.1, and in the sulphanilamide group 21.9 per cent. The frequency of otitis is the same in the sulphanilamide as in the control groups.

Peters and Havard (6) examined 300 patients, of whom half received no treatment and the other half were given proseptasine in doses of from  $3/4$  to 6 g daily for two days, then half the dose for two days. Of the 150 control cases, however, 56 received «anti-toxic» serum. The number of patients with complications in the control group represented 56 per cent., in the treated group 35 per cent.

Peters and Havard's results were criticized by Wesselhoeft and Smith (11), who pointed out that the frequencies of otitis and adenitis were the same in the two groups, and that the difference in the complication frequency arose chiefly from a higher frequency of albuminuria, arthralgia and endocarditis in the control group. Endocarditis occurred in 6 per cent. and in 2 per cent. of the cases in the control group and in the treated group respectively, which must be said to be a strikingly large number of patients with endocarditis; the frequency of this complication is usually stated to be less than  $1/2$  per cent. In the view of Wesselhoeft and Smith the large number of joint affections in the control group may be due to serum sickness. Finally, they decline to accept transitory albuminuria as a complication. In the two groups albuminuria occurs in 12.6 and 8 per cent. of the cases respectively. We must agree with Wesselhoeft and Smith that Peters and Havard's figures are unconvincing, yet the number of patients with complications is lowest among those treated with proseptasine.

Sako, Dwan and Platou (7) compared 100 cases of scarlet fever treated with sulphanilamide with 100 control cases. At the commencement the dose was 5 cg, and thereafter 3 cg per kg body weight per 24 hours. The duration of the treatment averaged

12 days; the best results were obtained when sulphanilamide was given all the time. The outcome of this study was that only 8 per cent. of the patients treated with sulphanilamide had complications, as against 41 per cent. of the patients in the control group, a very conspicuous effect. It must be added, however, that certain complications were markedly frequent in the control group, for example nephritis in 11 per cent. of cases; the frequency of nephritis is usually put at one or two per cent. During the milk epidemic in Copenhagen in 1939 Bojlén (12) found 1 per cent. of 293 cases, and Djørup (13) in the milk epidemic of 1917 1.3 per cent of 279 cases. Notwithstanding this objection, however, there can be no doubt that there was some effect from the treatment in Sako, Dwan and Platou's material.

Julius Strøm (8) reports on the results of 122 cases of scarlet fever treated with prontosil rubrum and 122 control cases at the Hospital of Epidemic Diseases, Stockholm. Prontosil was administered throughout the course of the disease; in both groups 22 also received serum. The doses were rather small, viz. under 3 years  $7 \frac{1}{2}$  cg  $\times$  3, from 3 to 10 years 15 cg  $\times$  3, over 10 years 30 cg  $\times$  3. He found that the primary pyrexia on an average lasted 1.3 days shorter than it did among those treated with prontosil. Of the latter group 37.7 per cent. had complications as compared with 56.6 per cent. in the control group, and it was mainly the »bacterial» complications, otitis, sinuitis, sec. anngina and adenitis, that were reduced in number. Strøm also gives a full account of the complications as a result of prontosil treatment.

Hamilton and Togasaki (9) studied the effect of sulphanilamide compared with that of convalescent serum. The number of patients with complications was 10.6 per cent. against 13.6 per cent.

Le Fèvre (10) treated »a large number» of patients with sulphanilamide. Only one had a complication (adenitis); there was no case of otitis, mastoiditis, nephritis or carditis.

Patersson (14), after treating 200 patients with sulphanilamide, states that »complications were only rarely observed».

Benn (15) compared 215 sulphanilamide-treated cases of scarlet fever with 195 control cases. The patients were all children under 10 years. The dosage was: from 0—2 years 0.75 g, from 3—7 years 1.5 g, from 8—10 years 3 g in 24 hours. Treatment was continued until the temperature had been normal for a week, and, in the

case of complications, as long as was considered necessary. Of the treated cases 15 per cent. had complications compared with 25.3 per cent. in the control group. Here again the complication frequencies chiefly reduced were those of adenitis and otitis.

Pfaffenbichler (16) treated 150 patients with prontosil and compared the results with 150 control cases. The dosage was: 15 cg  $\times$  3 under 2 years and 30 cg  $\times$  3 over 2 years. Of those treated, 53.4 per cent. had complications and of the control group 73.4 per cent. In this instance too it was the more severe complications (especially the bacterial) otitis, adenitis, that were reduced, whereas sec. angina was not reduced in number.

There are other authors, however, who have observed no definite effect on the complications.

Mitman (17) treated 355 patients chemotherapeutically and found no perceptible reduction of the complication frequency.

Schwentker and Waghlestein (18) among 300 patients found a greater number with complications among those treated with sulphanilamide (23.6 per cent.) than among the controls (16.6 per cent.). In a group treated with serum there were complications in 13.7 per cent. of cases.

Wesselhoeft and Smith (11) compared their results with those of Peters and Havard (6) and Schwentker and Waghlestein (18) and found no distinct reduction of the complication frequency (66 against 72 per cent.).

Rascoff and Nussbaum (19) treated 154 moderately severe cases of scarlet fever alternately with sulphanilamide, serum and serum + sulphanilamide, the remainder receiving no treatment. For children the maximum dose of sulphanilamide was 3.88 g and for adults 5.18 g. In these small groups the complication frequency was 14.6, 20, 15.7 and 30.9 per cent. respectively. Of 10 severe cases of scarlatina treated with serum and sulphanilamide 8 had complications. On this basis, and having regard to the small material, these authors would not venture to credit sulphanilamide with any definite effect on the complication frequency.

The conclusion to be drawn from this perusal of the literature is that sulphanilamide cannot be said to have any decisively demonstrated effect on the frequency of complications in scarlet fever, though several of the results argue that to some extent the

drug may prevent the occurrence of complications. It must be observed, however, that the number of patients examined in the various comparative groups is rather small on the whole, and that in only few of the reports the experiments are clear-cut; very often serum has been given either to those treated with sulphanilamide or to some cases in the control groups, so that it would be unjustifiable to draw conclusions too definite from the material available.

The literature on the treatment of scarlet fever with serum is very voluminous. Bang and Frederiksen (20) have made a careful study of this literature and have also gone through the material at the Blegdam Hospital, Copenhagen, for the years 1934—1935. Serum was not administered to patients systematically during this period, but only to those who were intoxicated on admission. The serum was the same as that employed now, »scarlet fever streptococcic serum», prepared by the State Serum Institute, manufactured in such a manner that it has a high and polyvalent content of antitoxin and bacterial antibodies. The said authors arrive at the conclusion that serum treatment has an excellent detoxicating — and possibly life-saving — effect on intoxicated scarlatina patients, as indeed was previously demonstrated in Denmark [Bie, Ahrend Larsen and Siggaard Andersen (21)], whereas it has hardly any effect as a preventer of complications. Works by authors who hold that they have demonstrated a complication-preventing effect from scarlatina streptococcic serum [especially by Kraus (22) and by Lucchessi and Bowmann (23)] will not bear close examination — according to Bang and Frederiksen — particularly as far as the control groups are concerned.

### Own Material.

In the period from January 1st to December 31st 1940 the patients who were admitted to the Blegdam Hospital with fresh scarlet fever (not complicated with other diseases) were treated alternately with sulphanilamide (sulph.), »scarlet fever streptococcic serum (sc.s.) and normal horse serum (h.s.). In addition, a group of patients received no treatment. Patients hospitalized on the first day were given sulph., those on the second day sc.s., those on the third day normal h.s., and those on the fourth day



no treatment. For the purpose of building up a large control material all patients admitted on Sundays and holidays received no treatment either. This cannot be seen to cause any undesirable effect on the respective groups into which the material has been divided.

When in addition to sulph. and sc.s. we decided to treat with h.s., it was for the purpose of finding out whether the effect of sc.s. was possibly dependent solely on its content of immune bodies. When we had treated about 100 patients with h.s. we discontinued it, considering that this material would suffice to provide an answer to the question. Thereafter we continued with sc.s., sulph., and no treatment alternately every third day. The two sera are both native, and the only difference is that the former is an immune serum. The following dosage was employed: up to 4 years 20 cm<sup>3</sup>, from 4 to 14 years 40 cm<sup>3</sup>, and over 14 years 60 cm<sup>3</sup>. Serum was injected intravenously when possible; in the other cases it was injected intramuscularly. The doses of sulph. were: under 4 years 30 cg  $\times$  4, from 4 to 14 years 60 cg  $\times$  4, over 14 years 90 cg  $\times$  4, for in all eight whole days from hospitalization. In all cases treatment was commenced immediately on admission.

It was stated above that we have solely included all cases of fresh scarlatina admitted to Blegdam Hospital in 1910; from this it appears that patients admitted in the desquamation stage do not figure in the material. Some few patients received sc.s. although hospitalized on a day when another treatment was scheduled, because on account of their bad condition we considered it inadvisable to omit it; this refers to only very few patients.

With regard to evaluation of the complications we applied the usual criteria; these will merely be mentioned as far as the more important groups are concerned, adding that the diagnoses were made throughout the whole period by the same three people.

Adenitis was diagnosed only when one or both angular glands — in rare cases other neck glands — were at least hazel-nut in size and were either tender or occasioned pyrexia.

Arthralgia was diagnosed when there was pain in one or more joints, lasting more than a few hours. There would always be pain on passive movement, pyrexia as a rule, but only rarely objective joint changes such as redness and swelling. Arthralgia being a frequent companion to serum sickness, this symptom in the two

serum groups has not been included as a complication when it appeared during or a few days before or after the presence of serum exanthema.

The complication otitis comprises only suppurating otitis, and, like the diagnosis mastoiditis and sinusitis, was in every case made by one and the same otologist. Rhinitis was diagnosed only if it set in later on, after a free interval subsequent to the rhinitis which often forms part of the acute syndrome. The complications otitis and rhinitis are epidemiologically important, as patients with these may be infectious as long as they have discharge from the ear or nose.

The diagnosis of myocarditis is supported on electro-cardiographic evidence; in most cases there was a prolonged P—Q interval, or low or isoelectric T-waves.

Finally, the group secondary pyrexia comprises principally only cases with increased temperature where this increase could not be attributed to any cause traceable by the diagnostic means available. It is not impossible, however, that cases may inadvertently have been included where the etiology for some reason or other has evaded registration (see later). This secondary pyrexia in most cases is only slight and transient. For the reason mentioned less importance must be attached to this group, but it is included for the sake of completeness.

If a patient had more than one complication, each one is included in its respective group.

The most important data are given in Tab. 1.

It will be seen that the material comprises a total of 1,347 patients, and that just under half — 616 — form the control group in which no treatment was given. The sulph. group and the sc.s. group are fairly equal in size, viz. 318 and 295 patients, whereas the normal horse-serum group is rather small, for the reason given above (118).

On the second line are patients with complications, comprising only those complications that set in during hospitalization, that is to say not those present on admission. The complication frequency, by which is understood the percentage of patients who during hospitalization manifested one or more complication, is shown on the third line. It will be seen that this percentage is lowest for the sulph. group, viz. 37.1; compared to the control group, 46.3,

Table 1.  
Principal Data of Material.

|   | No<br>treatm. | Sulph. | Se. S. | H. S. |
|---|---------------|--------|--------|-------|
| No. of Patients .....   | 616           | 318    | 295    | 118   |
| » » » with compl. less 1st & 2nd days ....                                  | 285           | 118    | 116    | 56    |
| » » » » » in % of all pts. in group .....                                   | 46.3          | 37.1   | 39.3   | 47.5  |
| » » » » » less sec. pyrexia .....   | 254           | 85     | 109    | 55    |
| » » » » » » » in % of all pts in group ..                                   | 41.2          | 26.7   | 36.9   | 46.5  |
| Total No. of compl. less 1st & 2nd days .....                               | 456           | 194    | 178    | 92    |
| » » » » » » » in % of all pts. in group ..                                  | 74.6          | 61.0   | 60.0   | 78.0  |
| » » » » » » » less sec. Pyrexia .....                                       | 425           | 162    | 171    | 91    |
| » » » » » » » in % of all pts in group .....                                | 69.0          | 50.7   | 58.0   | 77.1  |
| No. of deaths .....   | 1             | 1      | 0      | 0     |
| No. of pts with adenitis less 1st & 2nd days in % of all pts in group ..... | 19.0          | 11.9   | 14.6   | 23.7  |
| » » » arthrititis less 1st & 2nd days in % of all pts in group .....        | 5.2           | 3.5    | 3.4    | 5.1   |
| » » » otitis less 1st & 2nd days in % of all pts in group .....             | 8.8           | 3.8    | 9.5    | 15.3  |
| » » » mastoiditis less 1st & 2nd days in % of all pts in group .....        | 3.2           | 1.2    | 1.4    | 2.5   |
| Average duration of disease in days .....                                   | 36.6          | 33.2   | 34.8   | 36.2  |
| Duration of Pyrexia in days .....   | 4.1           | 3.0    | 4.1    | 5.0   |
| Average of scarlatina exanthema in days .....                               | 4.3           | 4.0    | 3.9    | 4.2   |

this is a distinct difference which on being treated statistically proves to be barely three times the standard deviation ( $M=0.0337$ ,  $D=0.092$ ). The effect stands out still more clearly when we look into which of the complications are particularly reduced by the sulph. treatment.

If when calculating the complication frequency we segregate the group secondary pyrexia, we see from the 5th line that the difference becomes still greater, 26.7 against 41.2. At the same time the apparent effect of scarlet fever streptococcic serum is reduced. Statistical treatment shows this difference to be just under five times the standard deviation ( $M=0.0317$ ,  $D=0.145$ ). It appears that secondary pyrexia is most frequent in the sulph. group, so that we must take into consideration the possibility that some of these cases may have been induced by sulph. itself («drug fever»). Of the 32 cases of secondary pyrexia in the sulph. group 24 occur before the 10th day (average 7th day), whereas in the control group 18 of 31 cases of secondary pyrexia occur before the 10th day (average 9th day). The remainder are spread over as much as 26 and 21 days respectively.

The frequency of secondary pyrexia is 10.1 in the sulph. group and 5 in the sc.s. group. Statistically this difference is 2.67 times the standard deviation, i.e. it is made probable — though not definitely established — that the difference is a real one, that it is due to sulph.

We consider it not unjustifiable to assume that at any rate in some of the cases in the sulph. group it was drug fever, and for this reason the group «secondary pyrexia» should be omitted when making comparisons between the sulph. group and the control group. The few instances of secondary pyrexia in the serum group are understandable, as any secondary pyrexia in this group will most often coincide with the onset of the serum sickness and therefore will be recorded as such.

There were two deaths in the material, one in the control group, the other in the sulph. group, corresponding to a lethality of 0.15 per cent., a rate that confirms the mild course of this scarlatina epidemic. The deaths being so few, no conclusions can be drawn from them as to the effect of the treatment instituted.

The two case records will be referred to briefly. The patient in the control group was a twelve year old boy, hospitalized from 1st to 19th November 1940. Apart from «stenosing laryngitis» a couple of times, he had previously been well. Hospitalized four days after onset of scarlet fever; general condition then unaffected and course normal, except for arthralgia on the 9th day lasting until the 17th day. Pyrexia then set in, with coughing and vomit-

ing, and there was haematuria. At the same time bilateral suppurating otitis media was diagnosed. He rapidly became worse; on the day of death the urine contained much blood, and vesica was palpable to umbilicus.

To our surprise autopsy revealed considerable retroperitoneal haemorrhage of an extent similar to that in uroplania. The musculature of the bladder was completely imbibed with blood and several centimetres thick.

The other case was that of a one year old boy, hospitalized from March 13th to 15th, 1940. Immediately on admission he was given sulph. 30 cg  $\times$  4. Previously well. The day before admission he had exanthema and the temperature rose to 40.5° C. His general condition described as unaffected on admission, but rapidly grew worse. In the twelve hours prior to death he had several fits with irregular and superficial respiration, during which he was very cyanotic. At a time when his temperature was between 39° and 40° C. death occurred without his presenting definite focal symptoms. No autopsy.

In the year 1940 there were four other deaths among patients with scarlet fever. These are not included in our material, as two had in addition morbilli on hospitalization, a third was admitted in the desquamating stage, and the fourth was a 22 year old woman who was pregnant in the eighth month: eleven days prior to hospitalization she had suppurative otitis with slight pyrexia. Next day she was highly febrile and in the course of the day labour began. That evening she gave birth to a stillborn girl and an hour later collapsed suddenly, death occurring after a few minutes. Autopsy revealed some ascites as well as fluid in the pleural cavities and in the pericardium. There were also petecchiae under the endocardium, on the liver and gastric mucous membrane, together with chronic myocarditis.

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The average duration of hospitalization is also shown in fig. 1. The difference between the various groups is no greater because all patients were retained in hospital at least until the 28th day of the disease for epidemiological reasons, so that an increased complication frequency would not necessarily be registered. Nevertheless we see that the duration was shortest in the sulph. group.

Table 2.  
All Complications.

|                              | No<br>treatment<br>616 pts. |                     |          | Sulph.<br>318 pts. |                     |          | Sc. S.<br>295 pts. |                     |          | H. S.<br>118 pts. |                     |          |
|------------------------------|-----------------------------|---------------------|----------|--------------------|---------------------|----------|--------------------|---------------------|----------|-------------------|---------------------|----------|
|                              | No. pts.                    | in % of<br>all pts. | No. pts. | No. pts.           | in % of<br>all pts. | No. pts. | No. pts.           | in % of<br>all pts. | No. pts. | No. pts.          | in % of<br>all pts. | No. pts. |
| Adenitis .....               | 117                         | 19.0                | 38       | 11.9               | 43                  | 14.6     | 28                 | 23.7                |          |                   |                     |          |
| Supp. adenitis .....         | 1                           | 0.2                 | 1        | 0.3                | 3                   | 1.0      | 0                  | 0                   |          |                   |                     |          |
| Arthralgia .....             | 32                          | 5.2                 | 11       | 3.5                | 10                  | 3.4      | 6                  | 5.1                 |          |                   |                     |          |
| Supp. otitis .....           | 54                          | 8.8                 | 12       | 3.8                | 27                  | 9.2      | 18                 | 15.3                |          |                   |                     |          |
| Mastoiditis .....            | 20                          | 3.2                 | 4        | 1.2                | 4                   | 1.4      | 3                  | 2.5                 |          |                   |                     |          |
| Sec. angina .....            | 38                          | 6.2                 | 20       | 6.3                | 6                   | 2.0      | 10                 | 8.5                 |          |                   |                     |          |
| Sec. rhinitis .....          | 51                          | 8.3                 | 16       | 5.0                | 17                  | 5.8      | 3                  | 2.5                 |          |                   |                     |          |
| Peritons. Abscess .....      | 8                           | 1.3                 | 1        | 0.3                | 6                   | 2.0      | 2                  | 1.7                 |          |                   |                     |          |
| Sinuitis .....               | 10                          | 1.6                 | 4        | 1.3                | 8                   | 2.7      | 2                  | 1.7                 |          |                   |                     |          |
| Nephritis .....              | 12                          | 1.9                 | 4        | 1.3                | 0                   | 0        | 2                  | 1.7                 |          |                   |                     |          |
| Albuminuria .....            | 1                           | 0.2                 | 1        | 0.3                | 1                   | 0.3      | 0                  | 0                   |          |                   |                     |          |
| Relapse .....                | 10                          | 1.6                 | 3        | 0.9                | 2                   | 0.7      | 0                  | 0                   |          |                   |                     |          |
| Pneumonia .....              | 1                           | 0.2                 | 3        | 0.9                | 1                   | 0.3      | 0                  | 0                   |          |                   |                     |          |
| Bronchitis .....             | 3                           | 0.5                 | 0        | 0                  | 3                   | 1.0      | 1                  | 0.8                 |          |                   |                     |          |
| Myocarditis .....            | 9                           | 1.5                 | 5        | 1.6                | 12                  | 4.1      | 3                  | 2.5                 |          |                   |                     |          |
| Panaritium .....             | 8                           | 1.3                 | 4        | 1.3                | 1                   | 0.3      | 2                  | 1.7                 |          |                   |                     |          |
| Impetigo .....               | 5                           | 0.8                 | 0        | 0                  | 2                   | 0.7      | 0                  | 0                   |          |                   |                     |          |
| Pyuria .....                 | 3                           | 0.5                 | 0        | 0                  | 0                   | 0        | 0                  | 0                   |          |                   |                     |          |
| Stomatitis .....             | 1                           | 0.2                 | 1        | 0.3                | 3                   | 1.0      | 0                  | 0                   |          |                   |                     |          |
| Icterus .....                | 0                           | 0                   | 2        | 0.6                | 1                   | 0.3      | 0                  | 0                   |          |                   |                     |          |
| Serous meningitis .....      | 2                           | 0.3                 | 0        | 0                  | 0                   | 0        | 0                  | 0                   |          |                   |                     |          |
| Sec. pyrexia .....           | 31                          | 5.0                 | 32       | 10.1               | 7                   | 2.4      | 1                  | 0.8                 |          |                   |                     |          |
| Glottisoedem .....           | 2                           | 0.3                 | 0        | 0                  | 0                   | 0        | 0                  | 0                   |          |                   |                     |          |
| Abscess .....                | 2                           | 0.3                 | 1        | 0.3                | 3                   | 1.0      | 1                  | 0.8                 |          |                   |                     |          |
| Conjunctivitis .....         | 1                           | 0.2                 | 1        | 0.3                | 1                   | 0.3      | 0                  | 0                   |          |                   |                     |          |
| Anæmia .....                 | 33                          | 5.4                 | 27       | 8.5                | 15                  | 5.1      | 9                  | 7.6                 |          |                   |                     |          |
| Hæmorrhagic. diathesis ..... | 0                           | 0                   | 1        | 0.3                | 0                   | 0        | 0                  | 0                   |          |                   |                     |          |
| Acut. laryngitis .....       | 0                           | 0                   | 1        | 0.3                | 1                   | 0.3      | 1                  | 0.8                 |          |                   |                     |          |
| No. of death .....           | 1                           | 0.2                 | 1        | 0.3                | 0                   | 0        | 0                  | 0                   |          |                   |                     |          |
| Total of complications ..... | 456                         | 74.6                | 194      | 61.0               | 178                 | 60.0     | 92                 | 78.0                |          |                   |                     |          |

viz. 3 to 4 days shorter than in the control group, though this rather marked difference is reduced somewhat when compared to the duration in the sc.s. group, which is 1.8 days shorter than in the control group. Finally, fig. 1 shows that primary pyrexia is

more than one day shorter in the sulph. group than in some of the other groups; this rather considerable difference might be used as an argument to show that sulph. after all is not entirely without effect on the toxic phase of the disease, which in that case could be explained by a more rapid destruction of the toxin-producing agents.

In Table 2 our intention is to show what the complications are and which of them are affected by the various treatments. As already stated, these complications can be divided more or less into toxic and bacterial, and it will be seen that, as might be expected, it is on the bacterial complications, more particularly on adenitis and otitis, that sulph. has an effect. It is of great importance that an effect on the cases of otitis can be demonstrated, for, by virtue of its frequency, long duration, danger, and risk of permanent invalidity in the form of reduced hearing or deafness, it is the most sinister of all complications in scarlet fever; and furthermore, as stated above, patients are infectious as long as there is any ear discharge. It will be seen that the adenitis frequency is 11.9 in the sulph. group and 19.0 in the control group, whereas in the groups sc.s. and h.s. the frequencies are 14.6 and 23.7 respectively.

As regards otitis, the frequency in the sulph. group is 3.8 compared with 8.8 in the control group, a considerable reduction which is additionally marked by the fact that the frequency in the sc.s. group and the h.s. group is 9.2 and 15.3 respectively. Statistical treatment of these figures shows the difference to be 3.2 times the standard deviation; if the two serum groups are lumped together with the control group the difference is 4.1 times the standard deviation. Thus it may be said that the observed reduction of the frequency of otitis in the sulph. group is a real one. For mastoiditis too there is a reduction, though less pronounced, as in the sulph. group the frequency is only 1.2 per cent. as against 3.2 per cent. in the control group, and 1.4 and 2.5 per cent. in the sc.s. and h.s. groups.

The distinct reduction of the frequency of secondary angina in the sc.s. group, compared with the fact that this is not observable in the sulph. group, and the low percentage of recurrences in the sc.s. group supports the now general opinion that for both secondary angina and recurrence it is not a question of a »fresh outbreak»

but of a re-infection, presumably with a new type of streptococci, a re-infection against which those treated with sc.s. are relatively protected.

The fact that sulph. was unable to reduce the frequency of secondary angina is presumably a result of its being a late complication; in our material the average day of occurrence is 23.2 and 23.7 in the control and sulph. groups respectively. (Table 3.) A continued medication with sulph. would presumably have reduced the frequency. We find that there was only one case of peritonsillar abscess (0.3 per cent.), which occurred on the 15th day in the sulph. group, against 8 cases (1.3 per cent.) in the control group, and here the average day of occurrence was 4.1.

The frequency of sinusitis is lowest in the sulph. group, and the same applies to the frequency of secondary rhinitis, except for the small h.s. group.

Among complications usually regarded as toxic is arthralgia, for which sulph. and sc.s. have the lowest and almost equal frequencies. It must be borne in mind, however, that for the serum groups the arthralgia figures are minimum values, which means that the frequency is probably lowest in the sulph. group.

Sulph. has no distinct effect on the frequency of nephritis. Here, however, the low frequency of the entire material must be taken into consideration, so that it would not be correct to ascribe to the serum treatment the circumstance that there was no nephritis in the sc.s. group.

The frequency of myocarditis is the same in the sulph. and in the control group, whereas it is highest in the two serum groups, which may perhaps have some connection to the frequent joint affections in association with serum exanthema (over 20 per cent.).

Finally, we have studied the duration of the scarlet fever rash in the four different treatment groups (Table 1). We find that in the sulph. group it averages 4.0 days, in the sc.s. group 3.9, in the h.s. group 4.2 and in the control group 4.3 days — i.e. there was no difference at all.

The other complications given in Table 2 call for no comment except in the case of simple anaemia, which will be referred to later.

Table 3 tabularizes the day of the occurrence of the complications within the various treatment groups. Here we find the



Table 3.

*Average onset-day of complications (except compl. occurring 1st—2nd days.)*

|                                | No. treatment |                   | Sulph. |                   | Sc. S. |                   | H. S. |                   |
|--------------------------------|---------------|-------------------|--------|-------------------|--------|-------------------|-------|-------------------|
|                                | No.           | Average onset day | No.    | Average onset day | No.    | Average onset day | No.   | Average onset day |
| Adenitis .....                 | 120           | 10.3              | 39     | 18.0              | 43     | 11.2              | 28    | 12.3              |
| Supp. adenitis .....           | 0             | 0                 | 1      | 17.0              | 3      | 7.6               | 0     | 0                 |
| Arthralgia .....               | 33            | 11.4              | 11     | 14.3              | 10     | 14.2              | 6     | 4.7               |
| Otitis .....                   | 54            | 14.7              | 12     | 18.2              | 27     | 15.8              | 18    | 14.3              |
| Mastoiditis .....              | 16            | 22.9              | 4      | 29.0              | 4      | 32.3              | 2     | 57.0              |
| Other complic. ....            | 156           | 16.3              | 86     | 18.3              | 58     | 17.7              | 23    | 17.4              |
| Other complic. less pyrexia .. | 126           | 17.7              | 53     | 23.4              | 51     | 17.4              | 22    | 17.2              |

interesting circumstance that in the sulph. group the complications set in later than in the control group and also later than in the two serum groups except for mastoiditis; this however is a late complication, and moreover only a few cases were observed.

This observation makes it probable that if the sulph. medication had been continued a further reduction of the complications might have been obtained.

In table 4 the material is divided into three age groups. It appears from the table that sulph. had not the same effect in the group 0—3 years as in the other two groups. This applies particularly to otitis, for which the frequency is 15.4 in the sulph. group against 13.0 in the control group. Nevertheless the frequency of otitis in the two serum groups is 19.2 and 26.3, so that one cannot entirely rule out the possibility that chance may have had some share in this. Indeed, this possibility is supported by the fact that in the age group 4—14 years the frequency of otitis is 1.0 in the sulph. group as compared to 8.4 in the control group, and in the age group over 15 years it is 0 against 4.3. This notwithstanding, it must be said to be striking that among the youngest children the sulph. effect was so much weaker than among the older ones and adults. We find the same phenomenon in connection with the treatment of other infectious diseases with preparations of the sulphonamide group; e.g. the effect of chemotherapeutic treatment on pneumonia and meningitis is less good in the low age groups. It would seem that the sulphonamides have

**Table 4.**  
**Age Groups versus Complication Frequency.**

[illegible]

Table 5.  
Complications with other Infectious Diseases.

|                  | No treatm't<br>(616 pts.) |     | Sulph.<br>(318 pts.) |     | Sc. S<br>(295 pts.) |     | H. S.<br>(118 pts.) |     | Total<br>(1347 pts.) |     |
|------------------|---------------------------|-----|----------------------|-----|---------------------|-----|---------------------|-----|----------------------|-----|
|                  | No.                       | %   | No.                  | %   | No.                 | %   | No.                 | %   | No.                  | %   |
| Morbilli .....   | 18                        | 2.9 | 6                    | 1.6 | 9                   | 3.1 | 1                   | 0.9 | 34                   | 2.5 |
| Tussis conv..... | 3                         | 0.5 | 2                    | 0.5 | 1                   | 0.3 | 1                   | 0.9 | 7                    | 0.5 |
| Varicellae ..... | 8                         | 1.3 | 4                    | 1.1 | 4                   | 1.4 | 1                   | 0.9 | 17                   | 1.3 |
| Diphtheria ..... | 2                         | 0.3 | 0                    | 0   | 1                   | 0.3 | 0                   | 0   | 3                    | 0.2 |
| Rubeolae .....   | 11                        | 1.6 | 4                    | 1.1 | 2                   | 0.7 | 6                   | 5.1 | 23                   | 1.7 |
| Enteritis .....  | 1                         | 0.2 | 0                    | 0   | 1                   | 0.3 | 1                   | 0.9 | 3                    | 0.2 |
| Influenza .....  | 1                         | 0.2 | 2                    | 0.5 | 0                   | 0   | 0                   | 0   | 3                    | 0.2 |
| Total .....      | 44                        | 7.1 | 18                   | 5.7 | 18                  | 6.1 | 10                  | 8.5 | 90                   | 6.7 |

less effect on small children than on older ones and adults; perhaps this is because a certain co-operation is required on the part of the organism, and presumably the youngest children are less capable of «doing their part» than older children or adults.

Another possible explanation of this strange circumstance might be found if the bacterial flora in otitis were not the same in the first years of life as later on. However, Dr. Johannes Nielsen, who is at present working on this question at the Blegdam Hospital, has kindly informed us that in all age groups pure cultures of haemolytic streptococci are obtained almost exclusively (98 per cent.) from pus of scarlet fever otitis.

Brief mention may be made here of the occurrence of other infectious diseases in patients with scarlet fever. Their nature and frequency are shown in table 5. The aggregate infection frequency is 6.7 and approximately lies on a level with the frequency of infections in scarlet fever in former years. With regard to the frequency of the various infectious diseases there is nothing remarkable except as far as diphtheria is concerned; here the frequency is strikingly low, 0.2, compared e.g. with Rolly's (24) material, which has a frequency of diphtheria of 5.6 out of 1,400 cases. It should be stated, however, that the constellation of scarlet fever-diphtheria at the Blegdam Hospital has been very low these last few years, a fact that is of course connected with the very low diphtheria morbidity of late.

### Complications from treatment.

Complications following upon treatment with sulphanilamide may be divided into those which occur at once: nausea, vomiting, cyanosis, lassitude, drowsiness, and those which set in only after treatment has lasted some time: drug fever, exanthema, anaemia, granulocytopenia, icterus, etc. Whereas it is reasonable to assume that the former are toxic, i.e. caused by a direct toxic action, it is probable that the latter symptoms are not toxic but allergic, i.e. caused by the uniting in the organism of sessile antibodies with an antigen. This question has been studied by Transbøl (24 a), who investigated complications from treatment with amidopyrine, salvarsan, gold preparations and sedormid. He arrived at the conclusion that complications appearing in conjunction with these drugs, especially granulocytopenia, haemolytic anaemia and thrombopenia, are allergic. This is supported by the fact that these symptoms never appear immediately, but only after several days have elapsed while the organism is being sensitised. Furthermore, they are not reactions that are capable of being induced promiscuously, but only in certain individuals and thus only in a minority of those who receive the drug; the one drug always causes the same reaction in the same individual, whereas the reaction is not necessarily induced by one of the other drugs, i.e. the reaction is specific. Finally, the reaction depends not on the size of the dose and consequently can be induced even by a small dose.

In contrast, the toxic complications occur in the majority of patients; they set in during the first few days, are directly proportional to the size of the dose and are more or less uniform for the same drug.

The complications that we have seen in association with sulph. treatment may accordingly be divided into two groups: toxic and allergic. Toxic complications consist of lassitude, drowsiness, cyanosis, headache, tinnitus, vertigo, nausea and vomiting. These symptoms were common and were manifested in the course of the first few days after treatment began. We have not enumerated them except as regards vomiting which, as fig. 6 shows, occurred in 7.2 per cent. of those treated, and had no visible relation to age. Only exceptionally was it so violent and frequent, and the

patient so intoxicated, that it was found necessary to suspend the treatment.

Of complications that presumably are of an allergic nature we have observed drug fever, exanthema and haemolytic anaemia.

«Drug fever» is no unusual complication of sulph. treatment. Long, Bliss and Feinstone (25) observed it in 9 per cent. of 307 sulph. treated adults and in 3 per cent. of 101 children. In a series of 100 patients Brown, Thornton and Wilson (26) found a frequency of 14, and Long, Haviland, Edwards and Bliss (27) a frequency of 10 in 1,000 patients. Of 250 cases Lockwood, Coburn and Slokinger (28) «frequently» observed drug fever, but «rarely» among children.

In our material this complication presumably is concealed in the group «secondary pyrexia», which is included as a complication of the scarlet fever infection itself. Indeed we have already suggested that one of the reasons why this complication is more frequent among sulph-treated patients than in the other groups (10.1 compared with 5.0, 2.4 and 0.9 per cent.) is this very fact. Only, it is so very difficult to decide whether an increase of temperature within the first two weeks of the infection has this aetiology or one that is quite different.

The same argument applies to a certain extent in respect of anaemia. Long, Bliss and Feinstone (25) say this complication is «common». Brown, Thornton and Wilson (26) found 7 per cent., Long, Haviland, Edwards and Bliss (27) 3 per cent. Wood (29) found 8.3 per cent. among children and 2.4 per cent. among adults. This complication too occurs more frequently in the sulph. group than in the others, viz. 8.5 per cent. as against 5.4, 5.1 and 7.6 per cent. By the way, the haemoglobin determination was not made as a matter of routine, but only when there were clinical signs of anaemia, so that as the distribution may be rather accidental, evaluation must be still more conservative.

Medicamental exanthema is a familiar complication, but the frequencies recorded vary a good deal. Long, Bliss and Feinstone (25) indicate 1.6 per cent. among adults and 3 per cent. among children. Brown, Thornton and Wilson (26) give 7 per cent., Long, Haviland, Edwards and Bliss (27) 1.9 per cent., Lockwood, Coburn and Slokinger (28) 3.2 per cent.

In our material (Table 6) the frequency is higher than in these

Table 7.  
Complications after Serum Treatment.

|        |                       |                         | Exan-<br>thema | Arthral-<br>gia |
|--------|-----------------------|-------------------------|----------------|-----------------|
| Sc. S. | 0-3 years<br>52 pts   | No. ....                | 31             | 9               |
|        |                       | % .....                 | 59.6           | 17.3            |
|        |                       | Average onset day ..... | 10.4           | 13.5            |
|        | 4-14 years<br>192 pts | No. ....                | 125            | 40              |
|        |                       | % .....                 | 65.2           | 20.7            |
|        |                       | Average onset day ..... | 11.2           | 12.7            |
|        | > 14 years<br>51 pts  | No. ....                | 33             | 21              |
|        |                       | % .....                 | 64.7           | 41.7            |
|        |                       | Average onset day ..... | 12.5           | 9.0             |
|        | 0-∞ years<br>295 pts  | No. ....                | 189            | 70              |
|        |                       | % .....                 | 63.9           | 23.7            |
|        |                       | Average onset day ..... | 12.0           | 12.3            |
| H. S.  | 0-3 years<br>19 pts   | No. ....                | 13             | 2               |
|        |                       | % .....                 | 68.4           | 10.5            |
|        |                       | Average onset day ..... | 10.4           | 11.6            |
|        | 4-14 years<br>73 pts  | No. ....                | 52             | 20              |
|        |                       | % .....                 | 71.2           | 27.4            |
|        |                       | Average onset day ..... | 9.6            | 13.4            |
|        | > 14 years<br>26 pts  | No. ....                | 18             | 3               |
|        |                       | % .....                 | 69.2           | 11.5            |
|        |                       | Average onset day ..... | 8.4            | 11.0            |
|        | 0-∞ years<br>118 pts  | No. ....                | 83             | 25              |
|        |                       | % .....                 | 70.3           | 21.2            |
|        |                       | Average onset day ..... | 9.5            | 12.4            |

In cases where anti-scarlet-fever streptococcic serum and normal horse serum were employed (table 7) we observed those complications that are usual after injections of heterologous serum, viz. primary serum shock and serum sickness consisting of exanthema, arthralgia and pyrexia. The whole syndrome is not necessarily present; there was nearly always exanthema, in most cases pyrexia, and often arthralgia. In this respect the frequencies were more or less the same for the two sera used in this material.

Primary serum shock was observed in only 3 cases, none of which were fatal, whereas transitory sickness in conjunction with the injection was somewhat more frequent.

The exanthema is very preponderantly urticarial and universal and in most cases accompanied by itching. Often there is some pyrexia, rarely exceeding  $39^{\circ}$ , and patients are somewhat affected. On an average the exanthema following anti-scarlet-fever streptococcic serum appeared on the 12th day; after normal horse serum between the 9th and 10th days. The frequency of exanthema is 63.9 for anti-scarlet-fever streptococcic serum and 70.3 for normal horse serum. In a certain number of cases serum exanthema occurred in direct association with the injection and again on about the 10th to 12th day.

The arthralgia cases were rather uncharacteristic. There was no perceptible preference for the large joints over the small ones. As a rule only one or two joints were affected. No demonstrable articular changes were observed, no direct tenderness, but there were pains with active and passive movements. Here again there was moderate pyrexia. The duration was from a few days to a week, in contrast to the scarlet fever arthralgia, which in most cases was considerably longer in duration. In the groups sc.s. and h.s. the average day of manifestation of serum arthralgia was 12.3 and 12.4 respectively, and, as might actually have been expected would be the case in both serum groups, only the arthralgia after sc.s. occurred with greater frequency in the adult group, viz. in 41.7 per cent. of the patients, whereas the total frequency of arthralgia was 23.7 and for h.s. 21.2.

In no case was arthralgia found without simultaneous exanthema.

From the above it will be seen that the complications from sulph. treatment in our material are much less frequent than those from serum treatment; what is more, they are less severe and less painful. In the two methods of treatment the risk involved is presumably greater with serum treatment, as in the latter case dangerous serum shock occurs more frequently than leucopenia and other serious complications from sulph. treatment.

No deaths are mentioned in any of the aforesaid works on sulphanilamide, though the materials are fairly large, 1,000, 408, 250 and 114 patients; among these were two cases of agranulocytosis.

It is difficult to get any exact figures from the literature of the frequency of primary serum chock. Boumann saw one case

of dangerous shock out of 2,000 injections, and Pfaundler reports three deaths out of 110,000 injections. The fact that primary shock is dangerous is shown by Heinstorf, who saw 147 cases, of which 8 died, whilst Kliwenko saw 33 cases with one death [quoted from A. Hübner (30)].

### Remarks on certain clinical features of the material.

In addition to examining the preventive effect of sulphanilamide against complications it has been the intention in the present work to study some of the clinical features of scarlet fever.

Having a rather large material of well-examined scarlatina patients we have endeavoured to obtain information on the following:

1. The relation of the general condition to the complication frequency.
2. The relation of exanthema and desquamation to the complication frequency.
3. A possible correlation between exanthema and desquamation.
4. Complication frequency in the various age groups.
5. Time of onset of the various complications.

The first three points are seldom mentioned in text-books and papers on scarlet fever.

For the purpose of elucidating the questions we have utilized our control material, which comprises 689 patients with scarlet fever; this figure also comprises those patients who had complications on being hospitalized, so that it is larger than the control group referred to in the foregoing, which did not include patients with one or more complications on the first or second day of admission. Immediately after admission we arranged our material into three groups on the basis of the general impression: unaffected, slightly affected and severely affected general condition. This was solely a clinical evaluation of the general condition and degree of intoxication, and certain features such as temperature had no influence on this evaluation. Furthermore, with reference to exanthema we divided the cases into four groups: None, slight, moderate and severe. By slight exanthema we understand a pale, finely punctate rash only on the abdomen and loins; by moderate



Table 8.  
*Degree Affected versus Complication Frequency.*

|                             | Un-affected | Slightly affected | Severely affected |
|-----------------------------|-------------|-------------------|-------------------|
| No. of Pts .....            | 595         | 93                | 3                 |
| » » » with Complic. ....    | 293         | 62                | 3                 |
| » » » » in % .....          | 49.2        | 66.7              | 100               |
| » » » » Adenitis .....      | 128         | 19                | 3                 |
| » » » » » in % .....        | 21.5        | 20.4              | 100               |
| » » » » Arthralgia .....    | 42          | 7                 | 0                 |
| » » » » » in % .....        | 7.1         | 7.5               | —                 |
| » » » » Otitis .....        | 62          | 21                | 0                 |
| » » » » » in % .....        | 10.4        | 22.6              | —                 |
| » » » » Mastoiditis .....   | 13          | 7                 | 0                 |
| » » » » » in % .....        | 2.2         | 7.5               | —                 |
| » » » » other Complic. .... | 188         | 58                | 4                 |
| » » » » » in % .....        | 31.6        | 62.4              | 100               |

a more diffuse and brighter red rash, and severe only the intensely red, almost universal rash.

Similarly we divided desquamation into slight, meaning characteristic but extremely limited peeling; moderate, more diffuse peeling for example on hands and feet or another area of the skin, and severe, the peeling of large pieces from hands and feet and on the body. On admission and throughout their stay in hospital the patients were examined at brief intervals with regard to the said symptoms by the same three people.

From table 8 it will be seen that in the material there are only 93 patients with slightly affected and only 3 with strongly affected general condition, which confirms the benignity of the scarlet fever occurring in Denmark at present. It appears that the complication frequency is much higher in the group slightly affected than in the unaffected group, as 66.7 per cent. of patients in the former had complications against 49.2 in the unaffected group. Statistical treatment of the figures reveals this difference to be greater than three times the standard deviation, so that the difference is a real one. It will also be seen that the higher frequency of complications is mainly due to otitis and mastoiditis and the group »other complications», whereas the frequencies of adenitis and arthralgia are almost equal in the two groups. All the three

Table 9.  
Complications versus Degree of Exanthema and Desquamation.

|   | Exanthema |        |      |        | Desquamation |        |      |        |
|---|-----------|--------|------|--------|--------------|--------|------|--------|
|   | 0         | Slight | Mod. | Severe | 0            | Slight | Mod. | Severe |
| No. of Pts .....                            | 83        | 309    | 280  | 19     | 134          | 243    | 298  | 16     |
| » » » with Complic. (+1. —2. day) .....     | 44        | 159    | 143  | 14     | 71           | 110    | 171  | 8      |
| » » » with Complic. (+1. —2. day) in % .... | 53.0      | 51.5   | 51.1 | 73.7   | 53.0         | 45.3   | 57.4 | 50.0   |
| Adenitis .....                              | 13        | 65     | 65   | 6      | 29           | 44     | 73   | 4      |
| » in % .....                                | 15.7      | 21.1   | 23.2 | 31.6   | 21.6         | 18.1   | 24.5 | 25.0   |
| Arthralgia .....                            | 6         | 14     | 25   | 1      | 4            | 14     | 30   | 0      |
| » in % .....                                | 7.2       | 4.5    | 8.9  | 5.3    | 3.0          | 5.8    | 10.1 | 0      |
| Otitis .....                                | 13        | 40     | 26   | 2      | 22           | 24     | 35   | 2      |
| » in % .....                                | 15.7      | 12.9   | 9.3  | 10.5   | 16.4         | 9.9    | 11.8 | 12.5   |
| Mastoiditis .....                           | 4         | 11     | 5    | 0      | 4            | 4      | 10   | 2      |
| » in % .....                                | 4.3       | 3.6    | 1.8  | —      | 3.0          | 1.6    | 3.4  | 12.5   |
| Other Complic. ....                         | 47        | 120    | 97   | 13     | 62           | 91     | 119  | 6      |
| » » in % .....                              | 56.6      | 38.8   | 34.6 | 68.4   | 46.3         | 37.4   | 40.2 | 37.5   |

patients with strongly affected general condition had complications. The higher frequency of complications in the group with slightly affected general condition, especially the more frequent occurrence of otitis, might perhaps be explained by the fact that there were unusually many children of the age group 0—3 years whose general condition on hospitalization was slightly affected. It now appears that the patients are so distributed over the age groups that group 0—3 years had 16.7 per cent., 4—14 years 8.1 per cent., and over 14 years 24.8 per cent. with slightly affected general condition on hospitalization. Thus the aforesaid higher frequency cannot have its explanation solely in the age distribution.

The high frequency of otitis among patients whose general condition was slightly affected seems to be in conformity with the observation that in «septic» scarlatina (where there always is severe necrotic angina) there is a particularly high frequency of otitis. This does not at all mean that the patients whose general condition we have described as slightly affected correspond to the clinical term «septic scarlet fever»; but presumably these were patients with relatively severe angina.

Table 10.  
*Degree of Exanthema versus Degree of Desquamation.*

|           |        | Desquamation |        |      |        |       |
|-----------|--------|--------------|--------|------|--------|-------|
|           |        | 0            | Slight | Mod. | Severe | Total |
| Exanthema | 0      | 18           | 40     | 22   | 3      | 83    |
|           | Slight | 82           | 114    | 111  | 2      | 309   |
|           | Mod.   | 34           | 85     | 154  | 7      | 280   |
|           | Severe | 0            | 4      | 11   | 4      | 19    |
|           | Total  | 134          | 243    | 298  | 14     | 689   |

Table 9 shows the relation of the degree of exanthema and desquamation to the frequency of complications. From this it appears that no correlation can be found. An almost equal number of patients had complications in the four different groups. No decisive importance can be attached to the higher frequency of complications in the severe exanthema group owing to the smallness of that group (19 patients). The frequency of otitis is highest in the group no exanthema and in the group no desquamation (15.7 and 15.4 per cent.) as compared with an average of 10–12 per cent. in the other three groups. The more frequent occurrence of otitis among patients without exanthema and desquamation may be explained, in part at any rate, by the fact that there are particularly many patients in the age group 0–3 years (in which otitis is most frequent) who either had no exanthema or no desquamation. In the group 0–3 years there are 17.4 per cent., from 4–14 years 8.9 per cent., and over 14 years 14.3 per cent. of the patients who had no exanthema while in hospital. The corresponding figures for patients without desquamation are 37.4, 12.5 and 15.8 per cent., i.e. a distinct preponderance for the lowest age group. It should be borne in mind, however, that the group no exanthema will include some patients who had exanthema before hospitalization.

Accordingly, nothing can be said of the risk of complications from the degree of exanthema or desquamation.

In tab. 10 exanthema is shown counter to desquamation for the purpose of ascertaining whether severe exanthema is accompanied by severe desquamation. The table shows that desquamation increases with more severe exanthema, but the relation is not particularly marked. Of patients with slight and moderate exanthema 82 of 309 and 34 of 280 respectively had no desquamation, and of 83 patients with no exanthema 40 had slight, 22 moderate and 3 severe desquamation; in these figures, however, will probably be a number of patients whose exanthema had disappeared before hospitalization, as already stated.

We have made the same examination of the group of patients who were treated with sc.s., it having been asserted that one effect of serum treatment was that desquamation became less severe. Our material has been unable to confirm this with certainty.

Table 4 shows the frequency of complications in the various age groups, the material having been divided into three age groups, viz. 0—3 years, 4—14 years inclusive, and 15 years and over. The table shows the lowest number of patients with complications in the group 0—3 years, 44.8 per cent., as against 46.1 per cent. in the group 4—14 years and 48.7 per cent. in the group 15 years and over. It appears furthermore that in the low age group otitis (and mastoiditis) occurs more frequently than in the other two age groups (13 per cent. against 8.4 and 4.3 per cent.); the complications secondary angina and secondary rhinitis are also more frequent in the lowest age group. On the other hand, arthralgia

Table 11.

*Average Onset Day of Complications in the Control Group.*

|                         |      |
|-------------------------|------|
| Adenitis .....          | 8.2  |
| Arthralgia .....        | 8.1  |
| Otitis .....            | 10.0 |
| Mastoiditis .....       | 23.0 |
| Sec. Angina .....       | 23.2 |
| Peritons. Abscess ..... | 4.1  |
| Sec. Rhinitis .....     | 19.0 |
| Nephritis .....         | 14.4 |
| Sinuitis .....          | 10.9 |
| Myocarditis .....       | 20.3 |
| Sec. Pyrexia .....      | 10.5 |
| Relapse .....           | 33.3 |

is rare in this group, whereas peritonsillar abscess and sinusitis do not occur at all here in this material. It should be added, however, that arthralgia is difficult to diagnose in the low age group, whereas among adults it is arthralgia that occurs with particular frequency (15.4 per cent.), besides peritonsillar abscess and sinusitis.

The frequency of nephritis, which is very low in our material, is of equal height in the three age groups. This age distribution of the complications is in agreement with the observations of other workers [Jochmann (31), Rolleston (32) and others].

Finally, the average onset days of the various complications are tabularized in table 11. The day is reckoned from the day of hospitalization, it having been impossible in several cases to determine the onset of the disease, and it was necessary to employ the same method of calculation for all cases. It must be remembered that this figure represents only the average onset day and was arrived at as the result of widely diverging times; for example, the average onset day of nephritis is 14.4, whereas this complication made its appearance at times varying from the first to the 35th day of the disease, with the majority lying between the 14th and 22nd day. Otherwise the results found do not differ from those of other investigations on this subject.

### Conclusion.

As the main result of this investigation it has been demonstrated that sulphanilamide has a complication-preventing effect in scarlet fever, especially on those complications that are usually regarded as bacterial — in this respect particularly the especially important complication otitis, and again the latter's sequel mastoiditis. The frequency of these two complications was 3.8 and 1.2 respectively when compared with the control group, in which it was 8.8 and 3.2. Adenitis was reduced by a third, as was arthralgia, peritonsillar abscess by three-fourths, and recurrences by about a third. Complications like sinusitis and nephritis were only slightly affected and myocarditis not at all (table 2). The circumstance which to our knowledge has not previously been observed, that sulphanilamide has only little or no effect on complications in the low age group (0—3 years), should also be mentioned (table 4).

The conclusion to be drawn from these results is that in the treatment of scarlet fever sulphanilamide medication should be a matter of routine, despite the drawbacks associated with it. The dosage we employed, however, a rather concentrated administration solely during the first week after hospitalization, should scarcely be maintained; for we have shown (see table 3) that, compared with the complications of the control group, those occurring in sulphanilamide-treated patients are retarded and in many cases only appear when the sulphanilamide must be presumed to have been excreted from the organism. It would therefore seem likely that continued treatment, possibly with reduced doses, throughout the first two or rather three weeks would have the effect of reducing the complications still more; we should therefore advise this, for example the full dose employed by us in the first week, and half the dose in the next two weeks. In that case the total dosage of sulphanilamide would be about 20, about 40 and about 60 g. respectively in the age groups 0—3, 4—14 and over 14 years, which must be considered as justifiable. It must be anticipated, however, that a larger number of those treated will have complications in conjunction with this treatment, as more of them will be sensitized. During the course of the treatment the patients must be carefully observed. A recurrence or an initial aggravation of the slight toxic symptoms will, like apparent or indubitable drug fever, indicate cessation of the treatment, as these symptoms may be the forerunners of more severe complications. Sulphanilamide exanthema is another indication for discontinuation. In general it may be said that there should be no hesitation in discontinuing the treatment on the manifestation of toxic symptoms, having regard to the fact that the treatment has an effect only in a certain number of cases.

It may be added that the epidemic in question was mild, so that the effect in future epidemics with perhaps more complications may stand out more clearly.

Whether or not preparations of the sulphapyridine or sulphathiazol group have an equal or greater effect cannot be said yet, but investigations on the subject are in progress at the Blegdam Hospital.

As regards anti scarlet fever streptococcic serum it will be seen that the total frequency of complications in this group is

reduced somewhat, and some complications not inconsiderably reduced, e.g. secondary angina, recurrence and adenitis, whereas the frequency of otitis is not affected; thus there seems to be no indication for routine serum-treatment, especially having regard to the fact that serum sickness is frequent (see table 7) and painful, and that primary serum shock too is relatively often present, and then always dangerous.

In this work we have obtained no clear impression of the well-known detoxicating effect of streptococcic serum; this is owing to the serum being employed as a matter of routine and thus in most cases being given to patients who were not intoxicated and had only slight pyrexia. Nevertheless there was almost always a distinct effect when it was administered to really intoxicated patients.

Serum in itself — i.e. in this case normal horse serum — cannot be seen to have had any complication-preventing effect whatever, though possible it was slightly detoxicating.

As regards complications from the treatment, we have endeavoured to divide them into toxic and allergic groups as far as sulphanilamide is concerned. The toxic symptoms — tiredness, nausea etc. — were common; vomiting was observed in 7.2 per cent. of cases. Of the allergic complications there was exanthema in 12.9 per cent., but never in the age group 0—3 years, which comprised 65 patients; nothing was seen of more serious reactions such as leucopenia, severe haemolytic anaemia and anuria.

Anti scarlet fever streptococcic serum caused serum sickness in 63.9 per cent. of the patients. Of these, all had exanthema, and 23.7 per cent. also had arthralgia. Serum shock was observed in 1 per cent. Complications after normal horse serum were rather more frequent.

Finally, a reference is made to certain particulars of the clinical picture of the scarlet fever epidemic in question. From this it may be deduced that there is direct proportionality between the degree of intoxication in the initial phase and the complication frequency, whereas there is no correlation between the latter frequency and the degree of exanthema and desquamation. An examination of the relation of the complications to the age of patients and of the average onset-day of complications revealed nothing new.

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From the Dep. II (Medicine) of the Kommune Hospital, Copenhagen (Chiefs: Professor H. I. Bing, M. D., and later, H. Heckscher, M. D.) and Dep. A of the General Laboratory of the National Health Insurance Physicians (Chief: Knud Brøchner-Mortensen, M. D.)

## Iron Content of Serum in Patients with Pernicious Anemia.<sup>1</sup>

By

KNUD BRØCHNER-MORTENSEN.

(Submitted for publication September 24, 1942).

In untreated patients with pernicious anemia a number of investigators have obtained increased or high normal values for the iron content of the serum (2, 5, 7, 8, 9, 11, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26). Among authors who have examined a fairly large patient material, Büchmann (5) found values over 200  $\gamma$  % in 4 out of 10 patients, Lederer (15) found such high values in 6 out of 8 patients, Moore, Doan & Arrowsmith (18) in 7 out of 11, de Raadt (19) in 6 out of 12 and Waldenström (25) in 14 out of 45. Only a few patients (6, 25) have given low normal or even subnormal values, which have been assumed to be attributable to complicating lesions, especially infection which is known to lower the iron content of the serum (4).

After the institution of liver therapy, the serum iron falls rapidly to subnormal values, and this fall appears to be one of the earliest recognizable effects of the treatment, as usually it commences before the rise in the reticulocyte count.

The values then keep at a low level for some length of time, whereafter they rise slowly to a normal level. Sometimes the serum

<sup>1</sup> The studies here reported have been carried out with the aid of a grant from «Kong Christian X's Fond.»

iron value keeps at a low level even for a considerable length of time (5, 7, 11, 13, 15, 18), especially in patients in whom the increase in hemoglobin percentage and erythrocyte count is slow.

### Writer's Investigations.

#### *Material.*

The material comprises 15 patients (4 men and 11 women) with untreated pernicious anemia.

One of these patients was admitted to Dep. VII of the Kommune Hospital, and 14 to Dep. II, representing all the untreated pernicious anemia patients but one who were admitted to this department in the period of August 1940—April 1942.

In 5 of these patients the symptoms had persisted for up to 3 months, in 8 between 3 months and 2 years, while 2 patients had been treated previously for pernicious anemia but not for the last 2 and 3 years respectively.

#### *Technique.*

Determination of the iron content of serum was carried out after Brøchner-Mortensen & Olsen's method (3).

The hemoglobin percentage was determined on hydrochloric acid hematin in Autenrieth's colorimeter, adjusted after Haldane's standard (100 % hemoglobin = 18.5 vol. % oxygen-combining power).

The color index was calculated after the formula:

$$\text{Color index} = \frac{\text{Hemoglobin percentage}}{\text{Erythrocyte count (millions/mm}^3\text{)} \times 21.4}$$

The volume index was calculated after the formula:

$$\text{Volume index} = \frac{\text{Volume percentage} \times 0.116}{\text{Erythrocyte count (millions/mm}^3\text{)}}$$

#### *Results.*

Prior to the institution of the treatment 7 patients showed over 200  $\gamma$  % serum iron, while the remainings 8 patients gave values falling within the upper half of the normal range (Table 1). In keeping with the findings in my previous studies (3) the limits for the normal variation of serum iron were set at 80—200  $\gamma$  %.

Of the 11 female patients 7 (Nos. 5, 7, 8, 10, 12, 13 and 15) were also suffering from complicating infections of the urinary passages

Table 1.

*Iron Content of the Serum in Patients with Pernicious Anemia before and under Treatment.*

| Pt. No. | Record No.   | Sex | Age | Hemo-<br>globin          | Serum iron                                  |                          |   |     |  |     |
|---------|--------------|-----|-----|--------------------------|---|--------------------------|---|-----|--|-----|
|         |              |     |     | Before<br>treat-<br>ment | Total<br>No. of<br>deter-<br>mina-<br>tions | Before<br>treat-<br>ment | First exami-<br>nation after<br>institution of<br>treatment |     | Lowest value<br>observed<br>under<br>treatment |     |
|         |              |     |     | %                        |   | γ %                      | γ %   | Day | γ %  | Day |
| 1       | II. 716/42   | M.  | 65  | 57                       | 5   | 256                      | 55  | 2   | 28   | 17  |
| 2       | II. 499/42   | M.  | 53  | 69                       | 5   | 245—218                  | 121   | 5   | 61   | 30  |
| 3       | II. 98—8/40  | M.  | 78  | 28                       | 17  | 230                      | 66  | 3   | 5  | 16  |
| 4       | II. 82—12/40 | F.  | 58  | 36                       | 9   | 230—196                  | 33  | 1   | 33   | 1   |
| 5       | II. 36—6/41  | F.  | 51  | 54                       | 5   | 215                      | 153   | 1   | 72   | 13  |
| 6       | II. 23—11/41 | F.  | 50  | 30                       | 8   | 214                      | 116   | 1   | 50   | 8   |
| 7       | II. 110—4/41 | F.  | 63  | 56                       | 7   | 202                      | 144   | 1   | 86   | 10  |
| 8       | II. 7—5/41   | F.  | 78  | 26                       | 13  | 185                      | 46  | 3   | 29   | 27  |
| 9       | II. 120/42   | F.  | 41  | 45                       | 9   | 180                      | 110   | 2   | 28   | 21  |
| 10      | II. 95—3/41  | F.  | 61  | 43                       | 7   | 163                      | 46  | 2   | 32   | 6   |
| 11      | II. 39—4/41  | M.  | 55  | 63                       | 11  | 159—145                  | 76  | 3   | 54   | 23  |
| 12      | II. 718/42   | F.  | 56  | 33                       | 7   | 150—123                  | 79  | 7   | 61   | 50  |
| 13      | II. 92/42    | F.  | 48  | 65                       | 2   | 146                      | 69  | 2   |  |     |
| 14      | II. 76—42    | F.  | 42  | 55                       | 2   | 138                      | 64  | 3   |  |     |
| 15      | VII. 91/41   | F.  | 57  | 33                       | 2   | 135                      |   |     | 52   | 20  |

associated with febrile phenomena, which may be assumed to have caused a relative decrease in serum iron. Complications were present in 5 of the 8 patients showing values under 200 γ %.

No demonstrable correlation was found between the values for hemoglobin and serum iron — a finding that is in conflict with the statement made by Waldenström (22, 23) about the iron content of the serum increasing with the severity of the anemia. In working up the findings reported in previous materials, one (18) is found to lend support to Waldenström's statement, while others (5, 15) furnish no evidence of such correlation.

During the treatment the serum iron was determined repeatedly (3—16 times) in 12 of the patients, only once in the remaining 3.

In this material the treatment has varied somewhat, as in some of the cases various stomach and liver preparations, inactive and active, were assayed as parts in other experimental series. The preparations used for the treatment proper in the present cases

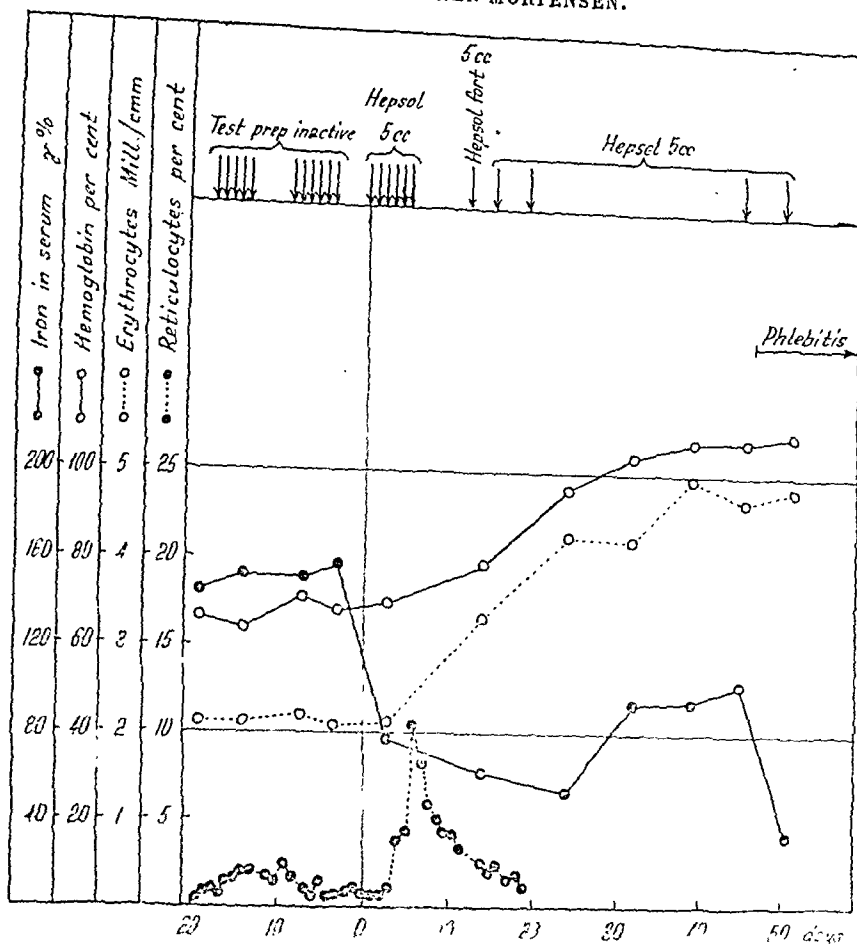


Fig. 1. Variations in serum iron in response to liver therapy in a patient with pernicious anemia (Pt. No. 11).

have most often been Hepsol or Hepsol fort. MCO (corresponding respectively to 5 g and 100 g of fresh liver per  $\text{cm}^3$ ) with varying dosage. The majority of the patients were discharged from the hospital for further treatment at home before complete regeneration was obtained.

All the patients showed a fall in the iron content of the serum in response to the treatment with an active preparation.

This fall in serum iron commenced very soon after the institution of the treatment. In 4 patients (Nos. 4, 5, 6 and 7) who were examined the day after the institution of the treatment, the fall in serum iron was respectively 163, 62, 98 and 58  $\gamma\%$  while 3 patients who were examined after two days showed a fall of respectively 210, 117 and 77  $\gamma\%$ . These variations are much greater than ever observed as spontaneous variations.

The rise in the reticulocyte count appears several days later. Among the 7 patients in whom the serum iron was determined within the first two days of treatment, the increase in reticulocytes commenced after 3—7 days (on an average, 4.1 days), and it reached maximum after 4—9 days (on an average, 6 days). The fall in

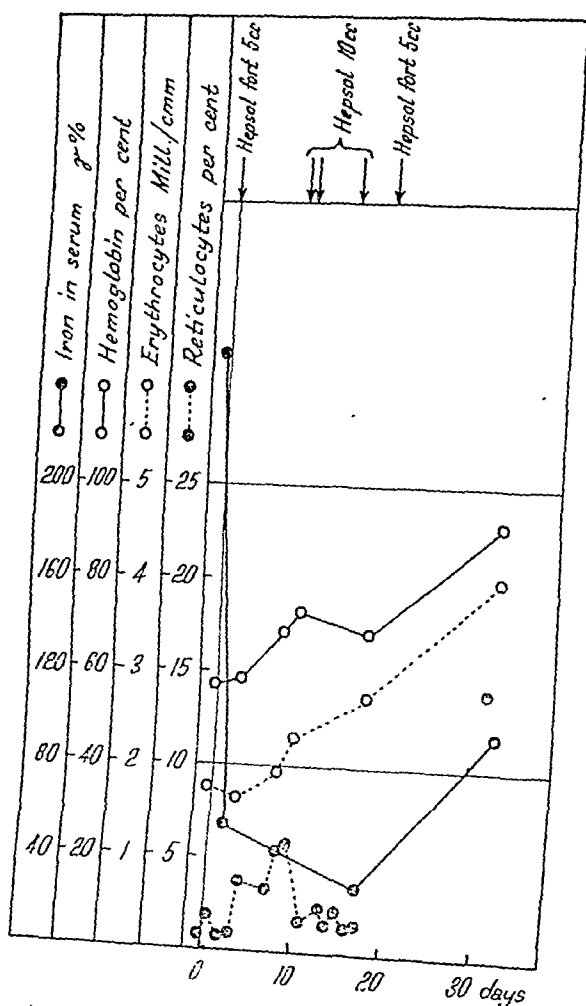


Fig. 2. Variations in serum iron in response to liver therapy in a patient with pernicious anemia. (Pt. No. 1).

serum iron is then to be considered a very early and reliable sign of the beginning therapeutic effect.

After this, the values for serum iron often decrease further for a shorter or longer period. Only one patient showed the lowest value within 24 hours. Among the 12 patients in whom at least 3 determinations were made after the commencement of treatment, 4 showed the lowest value within the first 10 days, the others later on.

In several cases the lowest values observed for serum iron were only a little under the lower limit for normal variations (80  $\gamma$  %). One patient (No. 3) showed a value as low as 5  $\gamma$  %, 5 patients gave values about 30  $\gamma$  %, and the rest gave values of 50  $\gamma$  % or more.

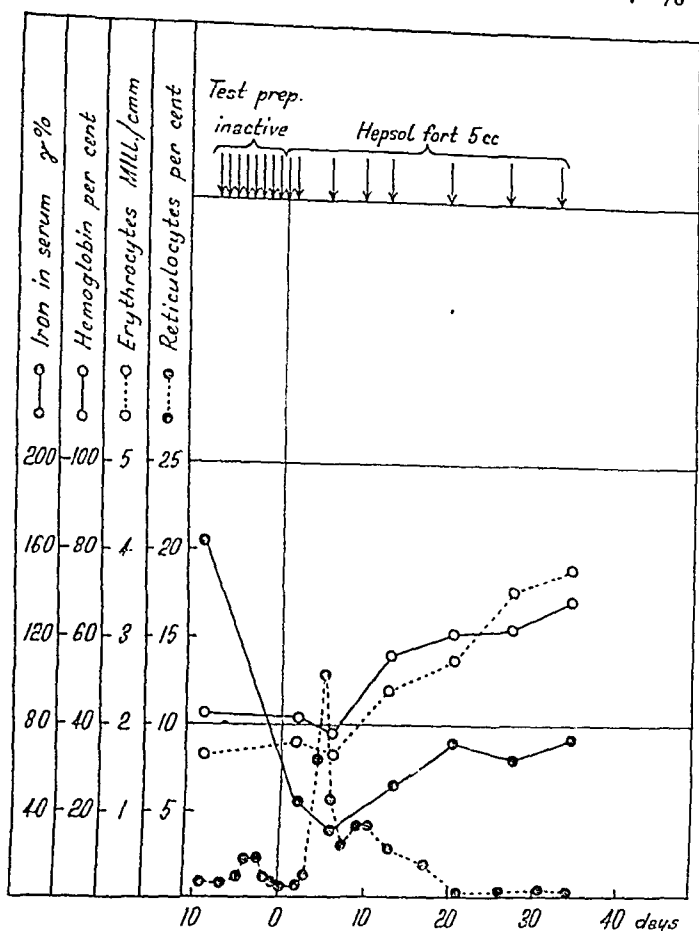


Fig. 3. Variations in serum iron in response to liver therapy in a patient with pernicious anemia. (Pt. No. 10).

Gradually, as the regeneration approaches its conclusion, the iron content of the serum rises again to a normal level (Figs. 1—3).

In patient No. 11 (Fig. 1) an inactive experimental preparation proved to have no effect. Administration of Hepsol, on the other hand, gave a fall in serum iron and a rise in reticulocyte count; and after treatment for about 1 month the patient showed 107 % hemoglobin, nearly 5 million erythrocytes/mm<sup>3</sup> and 103  $\gamma$  % serum iron. Then the patient had an attack of phlebitis, and the serum iron fell off again to subnormal values.

As a general rule the serum iron concentration keeps at a subnormal level as long as the hemoglobin percentage and erythrocyte count are decreased essentially. Only one exception to this rule was observed.

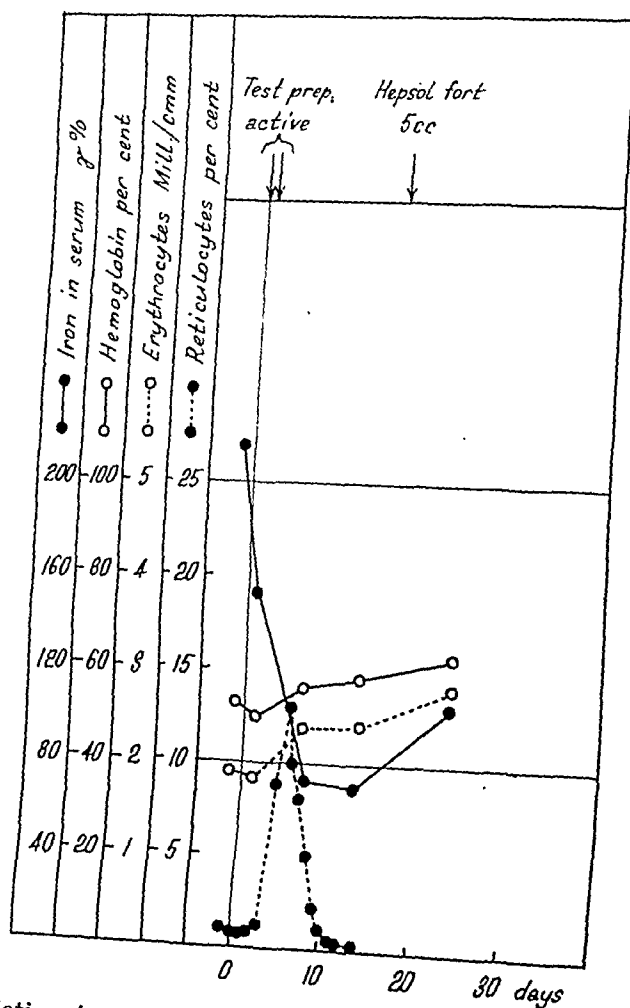


Fig. 4. Variations in serum iron in response to liver therapy in a patient with pernicious anemia (Pt. No. 5).

Patient No. 5 (Fig. 4) showed only slightly subnormal values for serum iron after the institution of liver therapy, and a rise to 106  $\gamma$  % at a point of time when the hemoglobin value was still 63. % and the erythrocyte count 2.61 millions. It may be that this patient had a high individual normal level.

When the treatment is discontinued or the intervals are made too long, so that the regeneration stops, the iron content of the serum increases again.

Patient No. 6 (Fig. 5) was given a single intramuscular injection of 5 cm<sup>3</sup> of Hepsol fort. MCO. In response hereto, the patient presented a fall in serum iron from 214  $\gamma$  % to 116  $\gamma$  % in the first 24 hours, and to 50  $\gamma$  % in 8 days, together with an increase in reticulocytes to 15.5 % in 4 days. There was a moderate rise in the

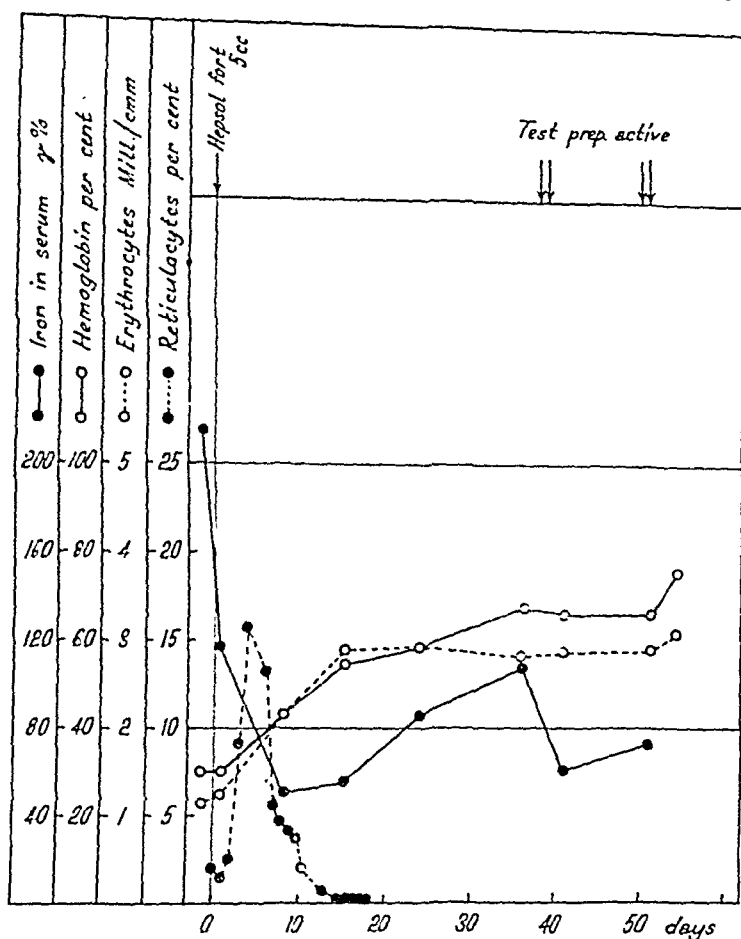


Fig. 5. Variations in serum iron on interruption of liver therapy in a patient with pernicious anemia. (Pt No. 6).

hemoglobin and erythrocyte values, but the regeneration subsided gradually, and after 35 days the serum iron had again increased to 106  $\gamma$  %. After resumption of the treatment with a slightly active experimental preparation there was again a moderate fall in serum iron.

It is a common clinical experience that the liver therapy in pernicious anemia not infrequently has to be combined with iron treatment in order to avoid hypochromic anemia.



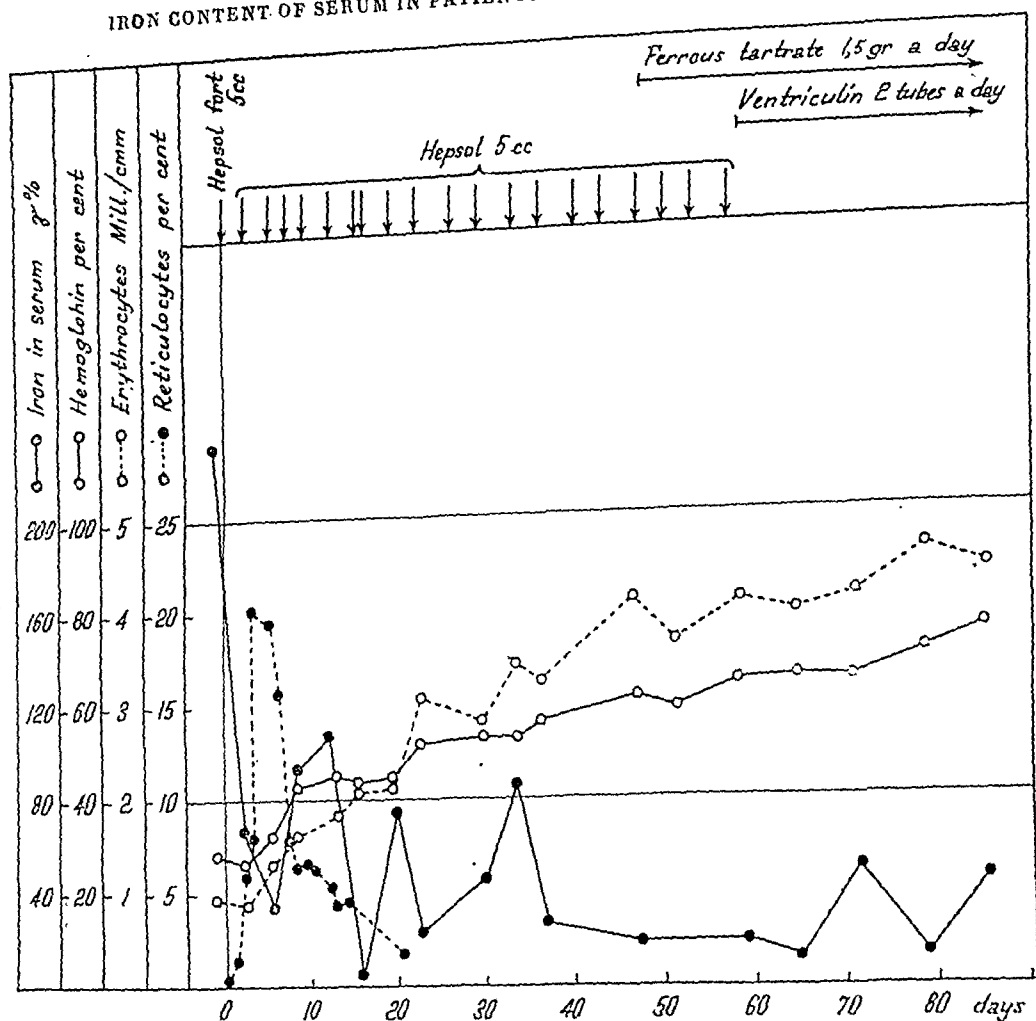


Fig. 6. Variations in serum iron in a patient with pernicious anemia in whom there appears to be iron deficiency. (Pt No. 3).

A striking illustration of this is seen in the case of patient No. 3 (Fig. 6), a man, 78 years old, who 3 years before this examination had been hospitalized for pernicious anemia. After his discharge from the hospital he had failed to keep on with the treatment, and on his present admission to the hospital the first examination showed: Hemoglobin 28 %; erythrocytes 0.92 million/mm<sup>3</sup>; color index 1.40; volume index 1.41.

After institution of liver therapy a fall was observed in serum iron from 230 to 33  $\gamma$  %, a rise in reticulocytes to 20.4 % and a lively regeneration. Very soon the anemia of the patient assumed a hypochromic character, and 48 days after the commencement of treatment he showed a color index of 0.68, while the volume index was 0.97. The color index did not rise again till iron treatment had

Table  
Tolerance Tests with Injection of 10 mg of Iron on a Control

| No.   | Record No.  | Diagnosis                  | Sex | Age | Height | Weight | Hemo-<br>globin<br>% | Sedi-<br>mentation<br>rate<br>mm/1 hr. | Tem-<br>per-<br>ature |
|---|-------------|----------------------------|-----|-----|--------|--------|----------------------|--|-----------------------|
| <i>I. Control material</i>                  |             |                            |     |     |        |        |                      |  |                       |
| 1   | II. 873/42  | Chron. constipation        | F.  | 19  | 174    | 66     | 98                   | 3                                      | norm.                 |
| 2   | II. 481/42  | Nil                        | M.  | 25  | 169    | 57     | 103                  | 2                                      | norm.                 |
| 3   | II. 448/42  | Myalgia                    | M.  | 29  | 179    | 78     | 93                   | 2                                      | norm.                 |
| 4   | II. 436/42  | Gastritis, slight          | M.  | 38  | 164    | 60     | 102                  | 3                                      | norm.                 |
| 5   | II. 1339/42 | Myalgia                    | M.  | 44  | 160    | 61     | 113                  | 2                                      | norm.                 |
| 6   | II. 1274/42 | Myalgia                    | F.  | 30  | 165    | 59     | 85                   | 4                                      | norm.                 |
| 7   | II. 498/42  | Fissura ani                | M.  | 20  | 176    | 72     | 100                  | 2                                      | norm.                 |
| 8   | II. 432/42  | Proctitis, slight          | M.  | 47  | 154    | 53     | 108                  | 3                                      | norm.                 |
| 9   | II. 798/42  | Neurasthenia               | M.  | 49  | 174    | 69     | 95                   | 4                                      | norm.                 |
| 10  | II. 832/42  | Obs. for duodenal<br>ulcer | M.  | 20  | 179    | 67     | 110                  | 5                                      | norm.                 |
| Variation                                   |             |                            |     |     |        |        |                      |  |                       |
| <i>II. Patients with pernicious anemia.</i> |             |                            |     |     |        |        |                      |  |                       |
| 1   | II. 716/42  | Pernicious anemia          | M.  | 65  | 176    | 86     | 57<br>57             | 4                                      | norm.                 |
| 12  | II. 718/42  | Pernicious anemia          | F.  | 56  | 164    | 62     | 41<br>62             | 26                                     | norm.                 |

been instituted. Examination of the serum iron showed a peculiar behavior: after the initial fall, some great irregular variations, and later markedly subnormal values (see below).

On the two last examined patients (Nos. 1 and 12) a tolerance test was made with intravenous injection of 10 mg iron (Ferrosi Lactas pro Inject. DAK) before and during the treatment (respectively on the 2nd and 12th day). The results are recorded in Table 2 and Fig. 7. Here, for the sake of comparison, the results are presented also for similar tolerance tests on 10 persons with a presumably normal iron metabolism.

In the two patients with pernicious anemia the tolerance test prior to the institution of treatment is seen to give a rise in serum iron that is lower than the corresponding rise in the control mate-

2.

*Material (10 Persons) and 2 Patients with Pernicious Anemia.*

Material (10 Persons) and 2 Patients with Pernicious Anemia.

| S e r u m i r o n $\gamma$ % |                   |         |                    |        |                     |        | Remarks                     |
|------------------------------|-------------------|---------|--------------------|--------|---------------------|--------|-----------------------------|
| Before inj.                  | 5 min. after inj. |         | 60 min. after inj. |        | 120 min. after inj. |        |                             |
|                              | Abs. value        | Rise    | Abs. value         | Fall   | Abs. value          | Fall   |                             |
| 179                          | 377               | +198    | 309                | — 68   | 282                 | — 95   |                             |
| 178                          | 440               | +262    | 370                | — 70   |                     |        |                             |
| 176                          | 342               | +166    | 298                | — 44   |                     |        |                             |
| 165                          | 378               | +213    | 287                | — 91   |                     |        |                             |
| 152                          | 318               | +166    | 286                | — 32   | 266                 | — 52   |                             |
| 145                          | 326               | +181    | 252                | — 74   | 220                 | —106   |                             |
| 125                          | 282               | +157    | 252                | — 30   |                     |        |                             |
| 120                          | 453               | +333    | 345                | —108   |                     |        |                             |
| 113                          | 323               | +210    | 277                | — 46   | 246                 | — 77   |                             |
| 100                          | 354               | +254    | 308                | — 46   | 265                 | — 89   |                             |
| 100—179                      | 282—453           | 157—333 | 252—370            | 30—108 | 220—282             | 52—106 |                             |
| 256                          | 331               | + 75    | 283                | — 48   |                     |        | Untreated.                  |
| 55                           | 284               | +229    | 131                | —153   |                     |        | After 2 days of treatment.  |
| 150                          | 274               | +124    | 266                | — 8    |                     |        | Untreated.                  |
| 73                           | 305               | +232    | 208                | — 97   |                     |        | After 12 days of treatment. |

rial — to maximal values a little below the maximal level for the controls. In one of the patients there is hardly any fall for one hour.

The tolerance test during the treatment shows a rise of normal magnitude. In the course of one hour there is then a fall which is a little greater than or at the upper limit of the observed in the control material.

So the variations in the iron content of the serum after intravenous injection of iron appear in pernicious anemic patients to deviate from the normal. But as only two patients were examined in this way, the results allow of no definite conclusion. These findings are recorded here, however, because apparently no similar examination has been reported previously.

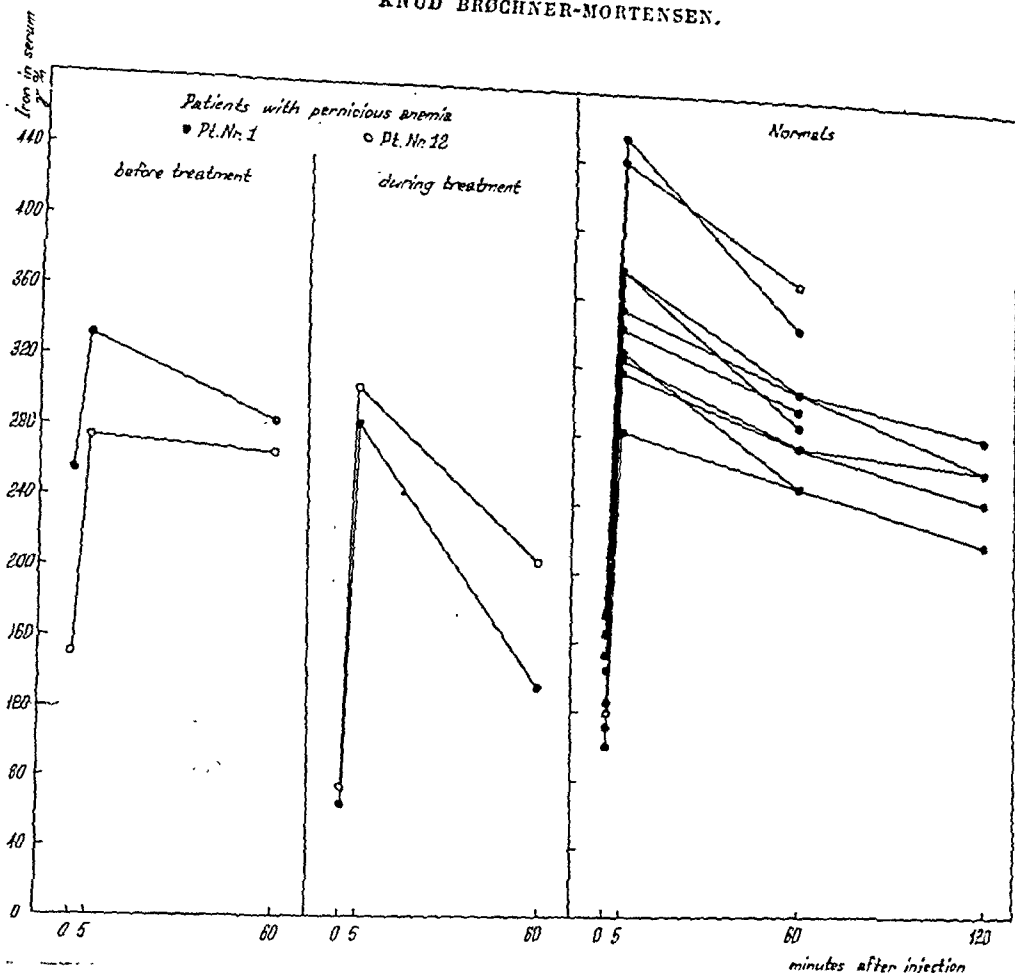


Fig. 7. Variations in serum iron on intravenous injection of 10 mg of iron in two patients with pernicious anemia before and during liver treatment, and in ten subjects without any disturbance in the iron metabolism.

### Discussion.

In keeping with previous findings, the present material has shown that in untreated patients with pernicious anemia the iron content of the serum is increased or keeps at a high normal level. In immediate response to the institution of liver therapy, and prior to the increase in reticulocytes, there is a rapid fall in serum iron to subnormal values, followed by a slow rise at the end of the regeneration.

Presumably the cause of the increased values for serum iron in untreated pernicious anemia is to be found in the circumstance that the liberation of iron through deterioration of erythrocytes is greater than the iron consumption in the hemoglobin formation under the defective maturing of the erythrocytes.

Presumably the fall in the values for serum iron after institution of liver therapy is due primarily to the increased hemoglobin formation but also to the less pronounced destruction of erythrocytes under this treatment.

Untreated patients with pernicious anemia usually present some very large amounts of iron stored up in the depots, in particular, the liver (1, 12). The subnormal values for iron observed immediately after the commencement of the treatment has to be taken, therefore, as due to the circumstance that the mobilization of the iron from the depots is lagging after the consumption of iron in the bone marrow. Under these conditions, the subnormal values for serum iron cannot reasonably be taken as an expression of iron deficiency as has been claimed (15). Nor does serum iron usually fall off to the very low values observed in patients with iron deficiency diseases as chronic hemorrhagic anemia or simple achylic anemia.

It is a different matter when we are faced by patients as the above-mentioned No. 3 (Fig. 6) in whom the values for serum iron fell off under the treatment to a very low level and remained very low through a considerable length of time, while also the hemoglobin regeneration had difficulty in rising over a certain level. In such cases it is reasonable to assume the presence of a genuine iron deficiency, as medicamental administration of iron soon will set the hemoglobin formation a-going again.

Presumably this condition occurs in patients whose depots are depleted from loss of iron by hemorrhage, etc., and in whom the presence of achylia has impeded a compensatory absorption of iron. Correspondingly, it will be particularly apt to occur in patients in whom the pernicious anemia has been preceded by a simple achylic anemia.

The large variations in the iron content of the serum observed in patient No. 3, and not seen in any previous case seem most likely to be attributable to irregular mobilization of iron from the depots or, perhaps, irregularities in the function of the bone marrow (the patient was 78 years old).

A similar sudden and transitory rise in the iron content of the serum has been observed by several investigators, (11, 13, 20, 21) in immediate connection with a considerable loss of blood as, for instance, hematemesis and blood-letting.

In untreated patients with pernicious anemia several authors (6, 10, 17, 19, 23) have often found flat or relatively low serum iron curves in tolerance tests with ingestion of iron. But the outcome of these tests has varied greatly in the various patients, and a collective evaluation of the findings is difficult because of differences in the experimental technique employed by the various investigators, and especially because of the rather scanty information given about control materials.

Repeated examinations on the same patients have shown a considerable higher rise in serum iron in such tests during the treatment than before (17, 19, 23). As a rule the maximum values observed have not been essentially higher after the treatment than before, and it is difficult to judge of the small differences as the long intervals between the sampling of the blood (1—2 hours) make it somewhat uncertain whether the real maximal value is observed.

Moore, Arrowsmith, Welch and Minnich (17) thought they were able from their experiments to conclude that the absorption of iron from the intestinal canal was inhibited in untreated pernicious anemia but set a-going again by liver therapy.

Waldenström (23) found the same difference in the iron absorption, however, on intramuscular injection of 10 mg of iron in the form of ferri ammonium citrate, observing about the same maximal values before and during liver therapy as reported by Moore and collaborators, and he thought, therefore, that also the iron depots exert some regulation of the serum iron: In untreated pernicious anemia, in which there is no demand for iron, the liver (possibly other depots too) retains the amount of iron supplied. Under liver treatment the administered iron is not retained but turns up in the serum.

In the intravenous tolerance test performed in the present work on two patients with pernicious anemia, we likewise find a slight rise in serum iron prior to the institution of treatment, and a greater rise under the treatment. According to the view advanced by Waldenström this outcome must be attributable to differences in the rate of depositing of iron in the depots. The more rapid fall in the values observed under the treatment will then be ascribable to increased iron absorption of the bone marrow.

### Summary.

1. The iron content of the serum is found to be increased to over 200  $\gamma$  % in 7 out of 15 untreated patients with pernicious anemia.

2. Immediately after the commencement of the liver therapy, several days before the increase in reticulocytes, there is a pronounced fall in serum iron, and the values keep at a low level till the end of the regeneration. On interruption of the treatment there is an increase in serum iron. Occasionally excessively low values for serum iron are seen under the liver treatment together with a low color index, indicating iron deficiency.

3. Intravenous iron tolerance tests on 2 patients show a slight rise and a slow fall in serum iron before the institution of liver treatment. Under the treatment the same test gives a normal rise in serum iron and a very rapid fall.

4. The causes of the variations observed in the iron content of the serum are discussed.

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(Aus der Neurologischen Klinik des »Serafimer-Lasarettet«, Stockholm.  
Chef: Prof. N. Antoni.)

## «Reine» Astereognosie, an zwei Fällen erläutert.<sup>1</sup>

Von

ERLAND MINDUS.

(Bei der Redaktion am 9. September 1942 eingegangen).

Auf der neurologischen Klinik sind kürzlich zwei Fälle von Astereognosie beobachtet worden, die der Erwähnung wert sein können. In so isolierter Form wie hier kommen sie verhältnismässig selten vor.

Die Erscheinung ist zwar bekannt, sie birgt aber immer noch viele ungelöste Probleme. Der vorige Weltkrieg brachte eine Menge Erfahrungen von solchen Störungen (Goldstein, Kleist, v. Walkenburger u. a.), aber im Hinblick auf das enorm grosse Material der traumatischen Läsionen, welche damals beobachtet wurden, kann diese Störung nicht als besonders gewöhnlich angesehen werden. In Kleists Sammlung von 74 Fällen von traumatischer kortikaler Sensibilitätsstörung kam eine isolierte Astereognosie nur viermal vor. Im übrigen wurde das Symptom meist bei Angiopathien beobachtet.

Wie bekannt, bezeichnet man mit Agnosie die Störung der Fähigkeit, Gegenstände wiederzuerkennen, ohne gleichzeitige wesentliche Störung der primären Sinnesfunktionen. Die gewöhnlichen Formen sind akustische, optische und taktile Agnosie. Eigentlich müssten hierzu auch agnostische Störungen des Geruchs und Geschmacks gerechnet werden. — Die taktile Agnosie kann ihrerseits in verschiedene Grade eingeteilt werden. Die schwerste Läsion

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<sup>1</sup> Nach einem Vortrag in der Ver. für int. Med. Stockholm. Febr. 1942.



liegt vor, wenn die Patienten die Konsistenz und das Material eines Gegenstandes nicht wiedererkennen können. Sie können nicht feststellen, ob ein Gegenstand hart oder weich, ob die Oberfläche rauh oder glatt, kalt oder warm ist. (Es können auch Schwierigkeiten vorliegen, das Gewicht zu schätzen.) Dieser Typ wurde von Wernicke in seinen grundlegenden Arbeiten als primäre oder apperzeptive Form bezeichnet. Der nächstschwere Grad, ziemlich ausschliesslich charakterisiert durch gestörte Formenauffassung, wird eigentlich als Astereognosie bezeichnet, obwohl diese Benennung oft alle Stadien der taktilen Agnosie decken muss. Bei dieser Form können die Patienten beschreiben, dass ein Bleistift aus Holz ist, lang, gerade, an einem Ende spitz usw., aber sie können ihn in keinem Fall als Bleistift identifizieren. Diese Form würde Wernickes sekundärer oder assoziativer Form entsprechen. Normalerweise hat man die Fähigkeit, die Form einfacher Gegenstände primär und unmittelbar aufzufassen. Geht dies nicht, so kann man durch Betasten von Ecken und Kanten die Form rasch erkennen. Der Astereognostiker kann weder das eine noch das andere. Der Schaden würde demnach bei ihm in einer Störung der Auffassung von Lage und Raum bestehen. Die zentralste Form dieser Agnosien wäre schliesslich die taktille Agnosie in der eigentlichen Bedeutung. Hierbei könnten die Patienten wohl Art und Form des Materials wiedererkennen, nicht jedoch den Gegenstand identifizieren.

In den beiden hier wiedergegebenen Fällen liegt eine Störung des Vermögens, Material und Formen wiederzuerkennen, vor.

**Fall 1:** S. A. W., 47jähriger Schwerarbeiter, in Behandlung in der Klinik 5.—22 Jan. 42. Inr. 12/42.

*Hereditär:* Keine Belastung.

*Frühere Krankheiten:* Zwischen dem 21. und 42. Jahre 3 Perioden mit ulcus duodeni. 1936 leichtes trauma capitis ohne Anzeichen einer cerebralen Einwirkung. Im übrigen immer gesund. Früher ziemlich reichlicher Alkoholgenuß, jetzt nur gering. 20 Zigaretten täglich. — Niemals irgendwelche Parästhesien in den Beinen oder Armen, kein erhöhtes Frostgefühl.

*Jetzige Krankheit:* Patient erwachte eines Morgens Anfang August 1941 und merkte, dass die rechte Hand unsicher war, er konnte die Knöpfe nicht zuknöpfen, liess die Semmel in die Kaffeetasche fallen, brachte das Geld nicht aus dem Portmonnaie heraus. Am Abend vorher hatte er sich wohlgefühlt und die ganze Nacht ausgezeichnet geschlafen. Auch jetzt keine Beschwerden wie Kopfschmerz, Müdigkeit oder Übelbefinden. Keine Schwäche in den Armen, nur mässig in der Hand. Kein Gefühlloswerden.

War schon nach ca. 2 Wochen besser, jedoch war der Zustand danach im grossen und ganzen stationär. Pat. ist demnach weiterhin belästigt von leichter Schwäche in der rechten Hand, und von ziemlich bedeutender Unsicherheit, die sich weniger geltend macht, wenn er mit den Fingern einen kleinen Gegenstand ergreifen will, jedoch mehr hervortritt, wenn er mit der ganzen Hand einen etwas dickeren Gegenstand ergreifen will, z. B. eine kleine Flasche oder die Brieftasche. — Er glaubt, auch etwas abgemagert zu sein. — Die poliklinische Beobachtung im Oktober ergab eine Bradycardie von 45/50 per min., Bldr. 100/80. Ekg. o. B. Unbedeutende Rachenasymmetrie, der rechte Gaumenbogen steht etwas tiefer. Keine Parese oder Sensibilitätsstörung, Dynamometer r. 33, 1.40. Erkennt mit der rechten Hand Münzen, berührt sie aber sehr unsicher, hat Schwierigkeiten beim Knöpfen. Reflexe o. B.

*Die Beobachtung in der Klinik* 5 Monate nach dem Insult ergab:

*Somatisch:* Ein etwas verbrauchter Astheniker mit etwas Gesichtasymmetrie. Bei den inneren Organen nichts Bemerkenswerthes ausser einer Bradycardie von tiefstens 50, welche später im Zusammenhang mit der Priscolbehandlung verschwand. Bldr. 90/60, Ekg. o. B. Periphere Gefässe o. B., Serologische Reaktionen, Blut- und Urinstatus o. B. —

*Psychisch:* Gutes Intelligenzniveau. Partialfunktionen intakt. Keine merkliche Ermüdbarkeit. Kein Zeichen von Aphasie.

*Nervenstatus:* Cornealtrübung im rechten Auge nach Trauma, Augenhintergründe o. B. Presbykusie, aber normale kalorische und rotatorische Reaktionen inkl. Kippreaktion. Angedeutete Kontraktur mit etwas stärker markierten Stirnfurchen über dem rechten Auge, aktive Innervation o. B. Kranialnerven im übrigen o. B. Die grobe Kraft überall o. B. mit Ausnahme einer etwas herabgesetzten Kraft beim Handdruck r. (Rechtshänder), Dynamometer r. 35, 1. 40. Keine Bajonettstellung oder Pronationstendenz. Diadochokinese und Finger-Nasenversuch werden ausgeführt o. B. und gleich bil. Oberflächensensibilität inkl. Ziffernschreiben und Vibration überall o. B., Pupillen- und Muskelreflexe o. B., Bauchreflexe vorhanden, keine Störung der Pyramidenbahn.

Prüfung auf Stereognosie: Pat. kann ein 1-Kronenstück und ein 2-Örestück wiedererkennen, kann zwischen einem 10- und 1-Örestück mit der r. Hand nicht unterscheiden. Ein Hosenknopf wird für eine Münze gehalten. Pat. identifiziert die Reibfläche einer Zündholzschachtel, einen Radiergummi, ein Messer, eine vierkantige Schachtel und einen Gummifinger. Eine mittelgrosse Haarnadel kann er weder nach Material oder Form beschreiben, noch weniger sie identifizieren. Während dieser Prüfungen kommt eine deutliche, aber nicht besonders schwere Unsicherheit zutage, Pat. lässt die Gegenstände ziemlich oft fallen. Das Bewegungsschema ist jedoch adäquat, und atetoide oder amorphe Bewegungen werden nicht beobachtet. Es ist deutlich, dass die Gegenstände, wenn sie zwischen die Finger genommen werden, leichter gehandhabt werden, als wenn sie in die Handflächen gebracht werden. Pat. selbst gibt an, dass es ihm verhältnismässig schwerer fällt, die Börse aus der Tasche zu holen, als mit den

Münzen selbst zu hantieren. Er besteht alle Apraxieproben zufriedenstellend.

Liquor, Schädelröntgen und Encephalogramm zeigen normale Verhältnisse, ebenso die Arteriographie im linken Carotisgebiet. Oszillometrische Untersuchung (Dr. Bringel) zeigt im rechten Arm doppelt so grosse Amplitude wie im linken. — Behandlung mit täglichen Priscolinjektionen (1 Amp. 2 mal) samt Übungsbehandlung.

2 Wochen nach der Einlieferung gab Pat. eine gewisse Besserung an. Auf besonderes Entgegenkommen von Prof. Katz wurde im Psychologischen Institut der Stockholms Högskola eine neue Stereognosieprüfung ausgeführt: diesmal wurde Grasset wie angedeutet auf der rechten Seite verzeichnet, ebenso leichte Pronationstendenz. Einstellung des rechten Arms bei geschlossenen Augen nach vorher eingenommener Lage mit dem linken Arm wird ausgeführt o. B. Auf gleiche Weise werden rotierende Bewegungen mit Arm und Hand zufriedenstellend ausgeführt. Flektion des r. Fingers 30 mal nacheinander in kürzest möglicher Zeit gelingt, nachdem der Übungseffekt erreicht ist, in 13.5', auf der l. Seite entsprechend 14.5". Entsprechender Versuch mit dem Mittelfinger r. in 14", l. in 15" (Untersuchender 6" bil.). Für die Daumen kommen die Werter. 11", l. 13.5" heraus. Pat. hat es auf der r. Seite schwerer, die Finger isoliert zu bewegen. Ein Knoten in einer Schnur wird schnell mit Hilfe beider Hände geknüpft. Nur mit der r. Hand allein geht es erst, nachdem das eine Schnurende fixiert wurde. Pat. gibt an, ein starkes Anstrengungsgefühl zu haben. Zufriedenstellend auf der l. Seiten. Beim Versuch rechts lässt Pat. die Schnur öfters fallen. Einen Kork aus einer weithalsigen Flasche herauszuziehen und wieder einzusetzen, gelingt mit einer Hand allein, mit der l. jedoch bedeutend schneller als mit der r. Auch hier Gefühl von Anstrengung in der r. Hand. — Das Ausschneiden eines kreisrunden Stückes von ca. 10 cm Durchmesser aus einem Papier wird zufriedenstellend ausgeführt bil., aber etwas besser mit der r. Hand. — Schreibt vorgelegten Text o. B. Schreibt seinen Namen und Stockholm mit offenen und geschlossenen Augen vollkommen leserlich. — Identifizierung von Gegenständen: Metallspule eines Schreibmaschinenfarbbandes: r. wird das Material als Bakelit angegeben; nachdem Pat. durch Kratzen mit dem Nagel vom Gehör geleitet wurde, wird das Material richtig bestimmt. Erkennt den Gegenstand nicht. Besteht die Probe links. Eine Zwirnrolle wird mit der l. Hand sofort erkannt. Mit der r. Hand wird weder Material noch Form identifiziert, er bezeichnet es als »Stempelhandgriff«. Ein Bleistift wird sofort mit der r. Hand erkannt. Eine dicke Glasbüchse: r. Hand: bezeichnet diese als »Stempelhandgriff«, kann das Material nicht angeben, l. o. B. Ein Stück Schreibkreide wird r. als aus Holz angegeben, die Form richtig bezeichnet, der Gegenstand nicht identifiziert. Links o. B. — Die Verschiedenheit zwischen Papieren mit ungleicher Rauigkeit wird richtig erkannt bil., auch bei kleinen Differenzen. Dasselbe glückt auch durch Palpation mit einem Federhalter (hier war jedoch vielleicht das Gehör etwas leitend). — Versuch, Unterschiede in der Stärke verschiedener Papiere festzustellen:

r. werden Differenzen aufgefasst zwischen 0.2 und 0.15 mm (normaler Schwellenwert: 1/100 mm). — Diskriminationsversuch mit Aesthesiometer: auf der r. Zeigefingerbeere ist der kleinste merkbare Abstand zwischen den Spitzen 2 mm, dasselbe 1. (Untersuchender weniger als 1 mm). Auf der Mittelfingerbeere: r. 4 mm, l. 2 mm. — Versuch mit Tremometer als Probe auf die feinere Koordination: Beim Entlangführen eines dünnen Metallstiftes in schmalen Ritzen, wobei jede Berührung der Ritzenwände durch eine elektrische Signalglocke als Fehler angezeigt wird, ist das Resultat — nachdem der Übungseffekt erreicht ist — 12 Fehler r., 10 Fehler l. (Untersuchender kein Fehler bil.).

Aus der hier wiedergegebenen Prüfung geht hervor, dass in konkreten und wohlbekannten Situationen, wie z. B. Unterscheidung zwischen Münzen, die Astereognosie sehr wenig hervortritt; dass aber, sobald die Situation ungewöhnlicher oder abstrakt ist, die Störung deutlich zum Vorschein kommt. Das beste Beispiel hierfür ist das besonders schlechte Resultat bei der Prüfung mit der Haarnadel. Feinere Präzisionsbewegungen mit den Fingern werden ziemlich gut ausgeführt, und die Sensibilität (Diskriminationsvermögen) ist sehr wenig gestört. Sobald die Ausgaben hauptsächlich die *vola manus* in Anspruch nehmen, kommen viel schlechtere Ergebnisse heraus (Erkennen einer Flasche, einer dicken Glasbüchse, die Handhabung der Börse, auch die Tremometerprobe).

*Zusammenfassung und Epikrise:* Ein 47jähriger Schwerarbeiter, ohne frühere Anzeichen einer Gefässerkrankung, erwacht eines Morgens, 5 Monate vor der Beobachtung, mit leichter Schwäche in der r. Hand und starker Unsicherheit, aber ohne Gefühlsstörungen. Gewisse Besserung. Bei der Beobachtung wird nichts wesentliches an den inneren Organen gefunden, der psychische Status ist ganz o. B. Etwas herabgesetzte Kraft in der r. Hand sowie Astereognosie wird beobachtet, aber keine Apraxie. Die Astereognosie tritt am ausgesprochensten hervor in *vola manus* und zeigt sich bei der Handhabung grösserer Gegenstände. Feinere Fingerbewegungen werden ziemlich gut ausgeführt, kleine Gegenstände einigermassen mit den Fingern identifiziert. In konkreten, wohlbekannten Situationen, wie bei Münzenprüfung, tritt die Astereognosie kaum hervor, aber bei abstrakteren oder ungewöhnlicheren Proben kommt sie deutlich zum Vorschein. Bei der Diskriminationsprobe erscheint eine minimale Sensibilitätsstörung in der r. Hand, die man mit gewöhnlichen Proben nicht nachweisen kann. Encephalogramm und Arteriographie zeigen nichts abnormes, nur die Oszillometrie zeigt eine der Bedeutung nach unklare Abweichung im linken Arm.

Die beobachtete Störung ist auf einen Prozess in der l. Hemis-

phäre hinzuführen, wahrscheinlich in der hinteren Zentralwindung und im gyrus supramarginalis. Nach Krolls Auffassung spricht die Abwesenheit von Apraxie für eine nur kortikal lokalisierte Störung. Hinsichtlich des Encephalogramms und Arteriogramms kann ein expansiver Prozess als weniger wahrscheinlich angenommen werden. Mit Hinsicht auf den Allgemeineindruck der Verbrauchtheit und vielleicht auch die beobachtete Bradycardie, die deutlich auf Priscot reagiert, ist die Läsion wahrscheinlich vaskulär bedingt.

**Fall 2:** J. V. 861/41, Ingenieur, geb. 1882, beobachtet auf der Neurologischen Klinik 9/10.—3/11 1941.

**Hereditär:** Vater mit 67 Jahren gestorben, an »Thrombose oder Arterienverkalkung«, im übrigen gesunde Familie, die hohes Alter erreicht hat.

**Frühere Krankheiten:** In den Kinder — und Wachstumsjahren gesund, aber viel Kopfschmerzen. Als Erwachsener hatte Pat. nur hier und da unbestimmte Digestionsbeschwerden. Seit vielen Jahren intensive Schlaflosigkeit, kam mit bemerkenswert wenig Schlaf aus. 1938 eine Periode mit Depressionen, Müdigkeit, Arbeitsunfähigkeit, die sich über einige Monate erstreckte. Weiterhin die gleiche Schlaflosigkeit. — Hatte sehr dringende und anstrengende Arbeit und gönnte sich niemals Erholung. Kein abus.

**Jetzige Krankheit:** Seit Sept. 40 bei einigen Gelegenheiten Augenflimmern, anschliessend Kopfschmerz. Febr. 41 bei einer solchen Gelegenheit für kurze Zeit Schwächegefühl im r. Arm. Merkte etwa einen Monat später hier und da aufkommende Gefühllosigkeit und Stechen in den Wangen. Bei einer Gelegenheit Absterben der ganzen r. Körperhälfte zusammen mit Ohnmachtsgefühl. Diese Sensationen dauerten ca. 15 Min. und wiederholten sich noch einmal am selben Tag.

**Aktualsituation:** 4/10. 41 beim Unkrautjäten, das ohne Anstrengung verrichtet wurde, plötzlich ein eigentümliches Gefühl im r. Arm, der ich wie tot fühlte, der Griff um die Hacke erschlaffte und der Arm fiel herunter, konnte aber immer noch aktiv bewegt werden. Die Kraft war deutlich herabgesetzt, aber Pat. vermochte doch gleich nachher, mit beiden Armen ein Bündel Gras wegzutragen. Der herbeigerufene Arzt konstatierte Ataxie in der r. Hand — Pat. konnte nicht knöpfen, die Hand nur schwer in die Tasche bekommen, schrieb seinen Namen mit grosser Schwierigkeit. Hatte Hitzegefühl und Kribbeln in der Hand sowie herabgesetzte grobe Kraft. Keine Sprachstörung. Der Blutdruck war 150 systolisch. Zwei Tage später war Pat. besser, hatte aber immer noch Schwierigkeiten bei Anzünden eines Streichholzes und konnte nicht knöpfen. Die Kraft im Arm kam allmählich zurück, ebenso verschwand das Gefühl, dass der Arm »wie tot« war. Kein Kopfschmerz, kein Erbrechen. Starke Müdigkeit.

*Beobachtung in der Klinik 5 Tage nach dem Insult:*

*Somatisch:* Guter A. Z., Pat. wirkt aber etwas müde. Gut erhalten. Innere Organe: Physikalische Herzuntersuchung erweist nichts besonderes, Herzröntgen ergab ein Volumen von 800 ml, per qm Körperoberfläche gerechnet 450 ml. Der Aortabogen war lang und gewunden. Bldr. 130/90. Periphere Gefässe weder rigid noch gewunden. (Durch ein Versehen wurde keine Ekg.-Untersuchung vorgenommen). Blut — und Urinstatus o. B.

*Psychisch:* Intelligenzniveau über dem Durchschnitt. Gutes Selbstbeobachtungsvermögen. Bedeutende Ermüdbarkeit. Dysphorische Gemütsstimmung. Partialfunktionen o. B., abgesehen davon, dass Pat. sich nur an 4 von 5 Sachen erinnert nach 3' Ablenkung. Sprechen manchmal etwas zögernd (soll immer so gewesen sein), mit subjektivem Gefühl der Schwierigkeit. Keine aphasischen Züge bei Prüfung. Schreiben nach Diktat und vorgelegtem Text geht gut, mit im grossen und ganzen der gleichen Handschrift wie vor der Erkrankung. Pat. gibt nur eine gewisse Schwierigkeit an, die Feder genügend zu fixieren. Praxieprobe s. unten.

*Nervenstatus:* Kranialnerven o. B. mit der Ausnahme, dass der r. Mundwinkel im Ruhezustand etwas tiefer steht als der l. Gute aktive Innervation. Motilität: Leicht herabgesetzte Kraft beim Handdruck rechts, Dynamometer r. 21, l. 32 (Rechtshänder). Bei Vorstreckung der Arme bei geschlossenen Augen Bajonettstellung auf der r. Seite. Keine Atrophieen. Diadochokinese wird bil. o. B. ausgeführt. Finger-Nasenversuch mit konstantem Falschzeigen r., o. B. l. Keine Bremsung. Knie-Fersenversuch o. B. bil. Sensibilität: Hautsens. o. B., die tiefe stark herabgesetzt in den Fingern der r. Hand. Vibration und Ziffernschreiben o. B. Stereognosieprobe: s. unten. Pupillen-, Muskel-, Bauch- und Cremasterreflexe o. B. Keine Störung der Pyramidenbahn. Keine Aufmerksamkeitsstörung hemianopischer Art.

Pat. kann mit der r. Hand weder knöpfen noch ein Streichholz anzünden, versteht den Inhalt der Aufgaben aber gut. Führt diese Bewegungen besser unter Kontrolle durch die Augen aus, aber auch dabei tritt bedeutende Ataxie hervor mit groben, unbeholfenen, amorphen Bewegungen. Wird ein Gegenstand vor ihm aufs Bett hingelegt, so kann er ihn mit einer gewissen Unbeholfenheit ergreifen. In die r. Hand gelegte Gegenstände werden nicht identifiziert hinsichtlich Konsistenz des Materials, Art der Oberfläche, und der Form. Eine Kugel wird nicht erkannt, Pat. gibt nur an, dass der Gegenstand keine scharfen Kanten hat, eine Taschenuhr wird nicht identifiziert, ein Bleistift kann weder erkannt noch beschrieben werden hinsichtlich des Materials und der Form. Ein Gummiring gibt ihm absolut keinen Begriff von der Konsistenz, noch weniger wird er erkannt. Das gleiche gilt bei Dingen wie Münzen, Feuerzeug u. a. — Die Lokalisation einzelner Reizungen geht langsamer und mit erhöhtem Schwellenwert auf der r. Hand, l. o. B. Die Diskrimination von zwei gleichzeitigen Reizungen ist deutlich herabgesetzt bei der r. Hand und Unterarm, auch nicht absolut einwandfrei 1.

Liquoruntersuchung, serologische Reaktionen und Schädelröntgen o.B. Die Encephalographie erweist keine sichere Ausweitung der Seitenventrikel, ferner auf der Konvexität innerhalb der r. Frontalregion eine Anzahl weiter Furchen, und l. in der Höhe des Bregma ein paar subarachnoidale Luftseen.

Nach ein paar Tagen, als die Müdigkeit deutlich geringer geworden war, konnte keine Herabsetzung der Tiefensensibilität mehr nachgewiesen werden. Bei ein paar Gelegenheiten gab Pat. Flimmersehen an, was einige Minuten dauerte. Danach glaubte Pat. einige Stunden lang, schlechter zu sehen, auch hatte er etwas Kopfschmerz. Dieser kam bei der geringsten Anstrengung wieder. Erhielt Acetylcholininjektionen morgens und abends.

Bei der Entlassung am 3/11. 41 wurde aufgezeichnet, dass sämtliche Armbewegungen sowohl bei geschlossenen als auch offenen Augen o. B. waren. Finger — Nasenversuch o. B. bil. Die Handhabung von Gegenständen geschieht mit ziemlich normaler Geschicklichkeit, die amorphen Bewegungen sind verschwunden. Pat. kann nun knöpfen: mit einiger Schwierigkeit bei offenen Augen, nicht bei geschlossenen; kann selbst den Schlips binden. Erkennt bei geschlossenen Augen mit r. Hand einen Bleistift, kann aber bei einem Glasstück und einem Radiergummi nur die resp. Konsistenz angeben, nicht die Formen. — Wenn der Untersuchende die Hände des Pat. berührt, kann dieser bei geschlossenen Augen die berührte Stelle bezeichnen, r. jedoch schlechter. Einfache Schmerzperzeption, Perzeption von Berührung und Temperatur o. B. Diskrimination von gleichzeitigen Reizungen geschieht mit etwas höheren Fehlerprozenten r., Pat. gibt auf der r. Hand wie derholt zwei Reizungen anstelle einer an.

*Zusammenfassung und Epikrise:* Ein 59jähriger Mann, dessen Vater möglicherweise an einer Gefässerkrankung gestorben ist, bekommt nach langjähriger Schlaflosigkeit und Prodromen (eine Depressionsperiode, schnell vorübergehendes Augenflimmern, Kopfschmerz und Gefühllosigkeit in der r. Körperhälfte) eine Parese und Ataxie im r. Arm. Diese bildet sich insultartig aus, ohne nennenswerte andere Symptome. Bessert sich nach einigen Stunden, aber bei Beobachtung 5 Tage später wird eine leichte Parese in der Hand wiedergefunden, eine rasch vorübergehende Störung der Tiefensensibilität, eine während der ganzen Zeit verbleibende äussere Sensibilitätsstörung (herabgesetztes Diskriminationsvermögen, erhöhter Schwellenwert für einfache Perzeption), sowie eine ausgesprochene Astereognosie. Im Status wird ausserdem ein Aortit und eine Rindenatrophie, die am ausgesprochensten auf der l. Konvexität ist, gefunden. Im Zusammenhang mit Bettruhe und Acetylcholinbehandlung gehen die Symptome bedeutend zurück.

Die Astereognosie ist jedoch bei der Entlassung immer noch deutlich vorhanden.

Auch hier dürfte die Störung auf die 1. Postzentralregion lokalisiert sein, wahrscheinlich auch gyrus supramarginalis. Im Hinblick auf die Abwesenheit von ideatorischer Apraxie ist sie genau wie beim vorigen Fall — wahrscheinlich als nur kortikal anzusehen. Ein expansiver Prozess kann nicht als wahrscheinlich angenommen werden. Im Hinblick auf den Aortiten sowie vielleicht auch auf die Gefässerkrankung des Vaters und auf die ankündigenden Flimmeranfälle handelt es sich wahrscheinlich um eine vaskuläre Störung. Der kommende Verlauf muss entscheiden, ob hier ein weiterer Fall von cerebraler Lokalisation von Buergers Krankheit vorliegt. Solche Fälle sind kürzlich ausführlich von Prof. Antoni beschrieben worden.

Nachschrift: 6 Monate nach der Beobachtung hat der Patient eine Hemianopsie bekommen.

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Von grossem Interesse ist die Beobachtung im ersten Fall, wo der Patient die Münzsorten erkennt, jedoch bei der Probe mit der Haarnadel versagt, wobei er nicht einmal die Art des Materials wiedererkennt. Dieses Phänomen kann ev. so ausgelegt werden, dass eine Haarnadel als Gegenstand schwerer zu erkennen ist als eine Münze, — aber eine solche Deutung erklärt nicht, dass der Patient auch die Art des Materials nicht identifizieren konnte. Nach meiner Auffassung ist die Erklärung eine andere: Die Störung ist verschieden intensiv in verschiedenen Situationen. Auf die Münzenprobe, die wohl eine der gewöhnlichsten Methoden ist, ist der Patient vielleicht mehr »eingestellt«, sie liegt ihm besser; und wenn man ihm mitten während dieser etwas vollständig unerwartetes gibt, etwas für seinen Horizont nicht so gewöhnliches, wie eine Haarnadel, so tritt der Schaden mehr hervor. Man kann sich von dem Eindruck nicht freimachen, dass es sich hier um ein Prinzip handelt welches auch bei Aphasien und kortikalen Sehstörungen beobachtet wird. Der Aphasiker kann z. B. in einem gewissen Stadium auf Befragen sehr wohl sein Alter angeben, aber die in Frage kommende Zahl isoliert, im unpersönlichen Zusammenhang, nicht nennen oder nachsagen. Der optisch Agnostische kann z. B. einen Ball ausserordentlich gut in Körbe werfen, die in verschiedenen Abständen



aufgestellt sind, aber er versagt vollkommen beim Versuch, den Abstand der Körbe von ihm zu schätzen. Also der Schaden ist in »konkreteren«, »ich-näheren Situationen weniger hervortretend als in »abstrakterem«, unpersönlicherem Zusammenhang. Ob diese Erscheinung zusammenfällt mit dem, was Goldstein als Störung der »Figur — Hintergrund« — Beziehung bezeichnet, ist ungewiss. Stimmt dies, so würde es sich diesenfalls um ein allgemeines Prinzip handeln, das sich bei verschiedenen zentralen Gehirnschäden wiederfindet.

Ein paar weitere Einzelheiten können des Hinweises wert sein. Die Beziehung der Astereognosie zu Sensibilitätsstörungen ist ein noch sehr umstrittenes Kapitel. Kleist will demnach die Störung absolut nicht zur Agnosiegruppe rechnen, sondern spricht von einem Auffassungsschaden, der nahe verwandt mit den Sensibilitätsstörungen wäre, und zitiert v. Valkenbergs Formulierung: »Hinterstrangtypus der kortikalen Sensibilitätsstörung«. Weizsäcker weist darauf hin, dass die gewöhnlichen Sensibilitätsuntersuchungen im allgemeinen ungenügend sind. Man findet darnach erhöhte Schwellenwerte bei der Perzeption, der Patient braucht längere Zeit bei der Untersuchung, und bei Ermüdung treten Störungen auf, die sonst nicht beobachtet werden können. Typisch hierfür ist der 2. Fall. Am Einlieferungstag, als der Patient sehr müde von der Reise war, und ausserdem irritabel und etwas herabgestimmt, hatte er eine deutliche Herabsetzung der Tiefensensibilität in den Fingern der kranken Hand. Einen Tag später, als er besser ausgeruht war, konnte diese Störung nicht wiedergefunden werden. Während der ganzen Zeit bestand er die Prüfung auf einfache Berührung, aber stets unsicherer und nach längerer Latenzzeit als auf der gesunden Seite. In beiden Fällen war das Diskriminationsvermögen herabgesetzt. Die hier beschriebenen Fälle beleuchten somit den Gesichtspunkt, dass Fälle, die initial als »reine« Astereognosiefälle imponieren, doch immer auch von einfachen Sensibilitätsstörungen begleitet sind. Lange stellt die Existenz einer »reinen« Astereognosie ganz und gar in Frage.

Die Fälle illustrieren auch einen Gesichtspunkt, den Plötzl formuliert hat mit »das mangelnde Erkennen vergiftet das Handeln«. Besonders in Fall 2 trat eine bedeutende Unbeholfenheit auf mit spreizenden, ataktischen, »amorphen« Bewegungen. Im ersten Fall trat dies nicht so stark hervor bei den feineren Fingerbewegungen

(Befühlen von Münzen, Schreiben), als beim Handhaben von etwas dickeren, in der Handfläche ruhenden Gegenständen. Hier war die ursprüngliche Parese fast ganz zurückgebildet, und die Unbeholfenheit stand in keinem Verhältnis zu der minimalen persistierenden Kräfteherabsetzung.

Interessant ist, dass der Schaden in beiden Fällen einseitig und auf die linke Hemisphäre verlagert war, ohne dass aphasische oder apraktische Störungen beobachtet wurden.

### Zusammenfassung.

Es werden zwei Fälle von taktiler Agnosie der rechten Hand geschildert. Bei beiden kamen die Symptome schlagartig ohne wesentlichere Begleiterscheinungen. Eine Analyse zeigte, dass die anscheinend »reine« Astereognosie doch von leichten Störungen der Sensibilität und Motilität begleitet war. Als Ursache wurden angiopathische Veränderungen angenommen. Im zweiten Falle handelt es sich möglicherweise um eine cerebrale Lokalisation der Buerger'schen Krankheit. An Hand der Befunde wurden die Ansichten Weizsäckers, Plötzls und Goldsteins kurz erwähnt.

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From the Medical Polyclinic, Rigshospitalet, Copenhagen, Professor,  
Dr. Med. Eggert Møller, Director.

## The Causes of Xerostomia.

By

MOGENS FABER.

(Submitted for publication September 19, 1942).

Most physicians will undoubtedly now and then find patients who complain of dryness of the mouth or pain in the tongue. An ordinary physical examination, however, will but rarely lead to an understanding of the complaint, nor will handbooks and periodicals be of much help. Since we have seen several of these patients at the Medical Polyclinic, it seemed natural to subject them to a closer investigation.

A study of the literature on reduced salivary secretion — xerostomia — shows a large number of single observations, frequently very interesting, but only few investigations which are capable of elucidating the causes of the symptom.

The first case is presumably that of Bartley from 1868, but the whole literature appears to comprise only 150 cases in all. In this country, cases are described by Arctander (1898), and later by Munck (1925), Germundsen (1933), Lange (1934), E. and T. Dalsgaard-Nielsen (1937) and Back (1940). Several cases are mentioned in Gravesen's doctoral thesis (1942) on lymphogranuloma benigna.

### *Methods and Normal Values.*

Two methods have been employed in the investigation of the salivary secretion. The most simple consists in placing a lump of sugar under the tongue of the patient, telling him to let it remain quietly, especially not to suck on it or make masticating motions. Measurement is then made of the time required for the lump of

sugar to dissolve. This time is about 15 minutes in young people with normal secretion, in older people 20 to 25 minutes, rising to 30 minutes in the very old. With a cooperative patient, this method can give reproduceable values, and is a rapid means of judging whether the salivary secretion is reduced. In most cases of even fairly pronounced xerostomia the lump of sugar will not be dissolved in 60 minutes. The test has the drawback, however, that normal or hyponormal values never are absolutely safe.

Lately we have collected the saliva quantitatively, using a bifurcated suction tube placed under the tongue. The patient must sit quietly — especially he must avoid swallowing. The saliva is collected in measuring cylinders under constant suction from a water jet pump adjusted to 40 cm water pressure. First the saliva is collected in 3 preliminary periods of 15 minutes each, in order to obtain the basal secretion. Then 2.5 mg of pilocarpine are injected subcutaneously, whereupon the saliva is collected once more in 3 times 15 minutes. This technique yields results which are very constant, both in the last two of the preliminary periods as well as from test to test. The values from the first period are nearly always too low, probably because of the psychic trauma which the patient suffers when coming to the laboratory. That the collection is complete is evident from the circumstance that the patient has no need of swallowing and frequently complains of pronounced dryness in the throat.

Fig. 1 shows data obtained from 30 normal persons. It will be seen that the basal secretion is 0.3—0.6 ml per minute, independent of sex and age. Following the pilocarpine injection the secretion rises to 1—2 ml per minute. This is not the maximal secretion that may be produced by means of pilocarpine, but is chosen in order to avoid that the pilocarpine causes any sweating which might inconvenience ambulatory patients.

### *Patients.*

The author's material now comprises 49 patients with dryness of the mouth. Of these only a minority have come to the Polyclinic with this particular complaint. The others have been found among the patients here, either through questioning when taking down their medical history or by subjecting all patients with parotid swelling, fissures in the corners of the mouth, or atrophied tongue

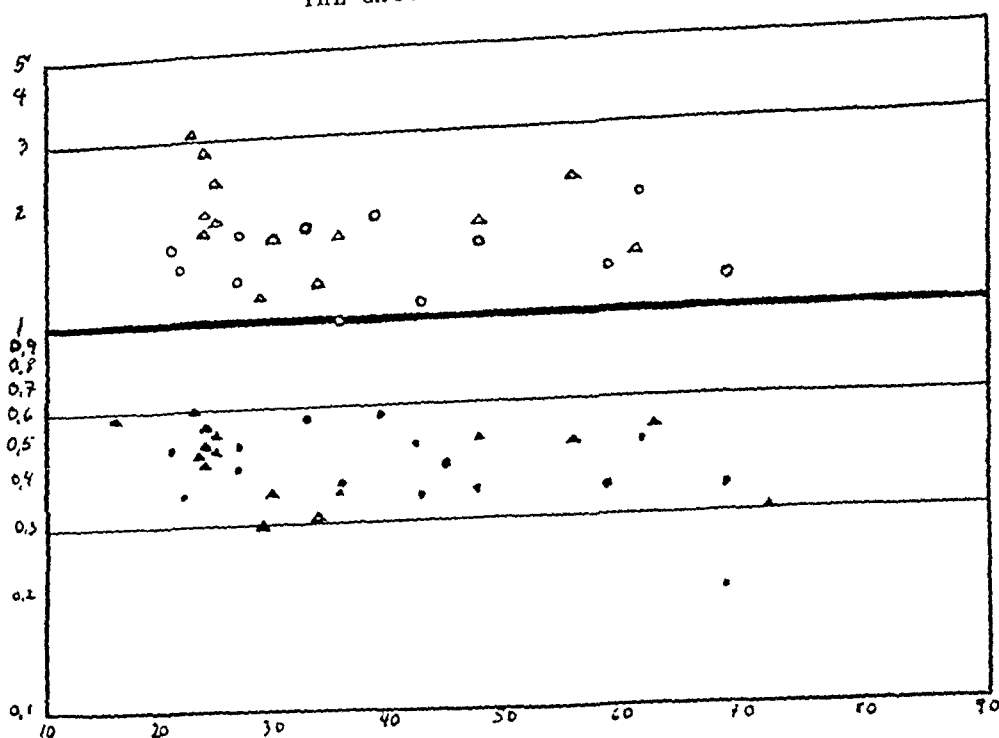


Figure 1.

The maximum salivary secretion per. minute before and after pilocarpine in 30 normals.

Men before ▲ after △ female before • after ○.

to further examination — at first by means of the sugar test, later with collection of the saliva. The cases in which the saliva has been collected are included in fig. 2.

In about one-third of these patients it was quite plain what was the cause of the dry mouth inasmuch as their salivary glands were diseased in various ways. In the rest of the cases, however, the cause of the xerostomia was not obvious.

### 1. Diseases of the Salivary Glands.

A 13-year old boy was referred to us for dryness of the mouth and extensive caries. Examination showed a total, presumably congenital aplasia of both parotid glands. The slight amount of saliva was mucous and originated presumably from the submaxillary glands. It hardly amounted to more than 5 ml in 1½ hours, in spite of the pilocarpine injection. This case seems to present an anomaly which is quite rare — at any rate, the author has been unable to collect more than 9 similar cases in the literature [Faber (1942)].

Decreased salivary secretion may be observed in parotitis epidemica [Massobrio and Boccuzzi (1935)]. The present author has met with 2 cases, both in adults. One showed normal secretion, but

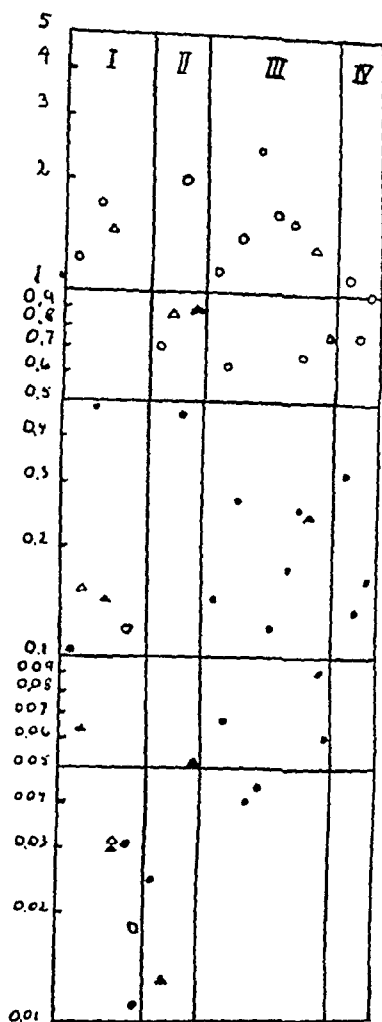


Figure 2.

The maximum salivary secretion pr. minute before and after 2.5 mg pilocarpine.

I. Inflammatory conditions in the salivary glands. II Pernicious anemia in relapse. III »Idiopathic» xerostomia. IV Untreated iron deficiency anemia.

Men before ▲ after △ pilocarpine female before • after ○ pilocarpine.

was not examined until late in the disease. In the other case, which was examined about 1 week after the beginning of the disease, a strongly reduced secretion was found, the basal secretion being 0.065 ml per minute. It rose but slightly after injection of pilo-

carpine, to 0.153 ml. In a renewed examination 2 weeks later the amount was still the same, even though the swelling of the glands was beginning to pass away.

A reduced salivary secretion may also be observed in case of other inflammatory conditions of the salivary glands. Thus Gravenstein found dryness of the mouth in one-third of the patients with lymphogranuloma benigna where swelling of the parotid glands occurred. The author has examined 2 patients of this type. Both showed reduced salivary secretion which again increased when the glandular swelling disappeared. In the one case where the saliva was collected no essential increase was found after pilocarpine injection, just as in the case of epidemic parotitis. In yet another case with parotid swelling (lymphogranuloma benigna suspected) the salivary secretion was found to be normal, and the patient did not complain of dryness of the mouth.

It is uncertain whether a permanent reduction of the salivary secretion follows lymphogranuloma benigna with swelling of the salivary glands. In a previous case at the Polyclinic the patient was dry in the mouth long after the swelling of the glands had disappeared, but more probably the cause was here to be found in the circumstance that the salivary glands had received X-ray treatment.

Other types of bilateral swelling of the salivary glands are also accompanied by decreased salivary secretion. We have examined 7 patients of this kind, of which the majority showed the picture of Mikulicz's syndrome. Of these patients, 6 had reduced salivary secretion. In one case the diminution had lasted 17 years, but here too the glands had received X-ray treatment. The decreased salivary secretion which was observed in these cases with inflammation of the salivary glands appeared to be extraordinarily massive. It was striking, at any rate, that in several instances almost no increase in secretion was observed after pilocarpine injection, in contrast to what is found when the reduced secretion has other causes.

Except for the 2 cases mentioned, the author can present no patients who have received X-ray treatment of the salivary glands, but that the secretion may fall in consequence of this treatment is well known [Hermann (1937)].

## 2. Pernicious Anemia.

The author has examined a total of 9 cases of untreated pernicious anemia. Of these, 3 showed neither subjective nor objective mouth symptoms, i. e., neither glossodynia nor glossitis, and the salivary secretion was found to be normal. Of the rest, 5 had reduced secretion. Of these, 3 showed atrophy of the tongue, 4 glossodynia, 2 also reduced lacrymal secretion. In the 9th case the tongue was atrophied, but the sugar was dissolved in 7 minutes, and no collection of the saliva was undertaken. 2 cases which were examined during treatment showed rapid restitution of the salivary secretion. In one, the sugar dissolving time dropped from 20 to 14 minutes, in the other from 52 to 20 minutes, both in the course of 14 days' treatment.

In addition, examination was made of 2 cases of anemia in pregnancy with megalocytic sternal marrow. In both cases the salivary secretion was found to have decreased. In one of them it became normal under liver treatment, though without hematologic remission. In the other it did not become normal until a simultaneously existing iron deficiency was counteracted. It is also stated that decreased salivary secretion may be observed after sprue [Marhoff (1938)], but the author's material does not include sprue patients.

## 3. «Idiopathic» Xerostomia.

There now remains a group of 26 patients of whom it may be said that it is not directly manifest why the salivary secretion has

Table 1.

Distribution according to age and sex of 26 cases of «idiopathic» xerostomia.

| Age in years | Women | Men | Total |
|--------------|-------|-----|-------|
| 10—20 .....  | 1     | 0   | 1     |
| 20—30 .....  | 0     | 0   | 0     |
| 30—40 .....  | 4     | 2   | 6     |
| 40—50 .....  | 6     | 1   | 7     |
| 50—60 .....  | 6     | 0   | 6     |
| 60—70 .....  | 3     | 1   | 4     |
| 70—80 .....  | 1     | 0   | 1     |
| above 80 ..  | 1     | 0   | 1     |
| Total        | 22    | 4   | 26    |



Table 2.  
Symptoms in 26 patients with «idiopathic» xerostomia.

| Symptom                                 | Present | Absent | Not examined |
|---|---------|--------|--------------|
| Subjective xerostomia .....             | 19      | 3      | 0            |
| Sialorrhea .....                        | 2       | 20     | 0            |
| Fissures in the corners of the mouth .. | 16      | 7      | 3            |
| Glossodynia .....                       | 14      | 4      | 8            |
| Papillatrophica of the tongue .....     | 7       | 17     | 2            |
| Lack of teeth .....                     | 11      | 7      | 8            |
| Dysphagia .....                         | 0       | 22     | 4            |
| Reduced lacrimal secretion .....        | 6       | 6      | 14           |
| Reduced stomach secretion .....         | 6       | 8      | 12           |
| Reduced hemoglobin percentage ..        | 0       | 25     | 1            |
| Reduced serum iron .....                | 2       | 9      | 15           |
| Vascularization in cornea .....         | 2       | 8      | 16           |

decreased. The distribution according to age and sex is recorded in table 1, while the most important symptoms are listed in table 2.

Subjective dryness of the mouth was found in practically all cases. 2 of the patients complained of salivation, mostly at night, but showed reduced secretion when the saliva was collected. Since the first collected portion in both cases was larger than the later portions — an exception to the rule — it must be assumed that it was due to lack of swallowing of the small amount of saliva. In one of the patients the subjective dryness seemed to vary more than the measurable saliva. Only one patient showed larger spontaneous fluctuations in the salivary secretion during the period of observation. But the author has seen several patients who stated previously to have been drier in the mouth; when the saliva was collected they nevertheless showed maximally reduced secretion. It may be added that the symptom appears to last for years. Some of the older patients have had it for more than 10 years, others only 3 to 4 months. No spontaneous cure has been observed in any of these patients.

In more than one-half of the patients fissures have been observed in the corners of the mouth, and the same number have complained of pains in the tongue. In about one-fourth of the patients we found a more or less pronounced atrophy of the mucous membrane of the tongue. Only one-third of the patients had their teeth pre-

Table 3.

Amount of saliva collected in patients with «idiopathic» xerostomia during treatment with riboflavin.

| No. | Date    | ml of saliva per min. in 15 min. periods<br>before and after injection of pilocarpine<br>subcutaneously |      |      |       |       |      | mg of<br>riboflavin |
|-----|---------|---|------|------|-------|-------|------|---------------------|
|     |         | before  |      |      | after |       |      |                     |
|     |         | 1   | 2    | 3    | 1     | 2     | 3    |                     |
| 1   | 11. V   | 0.23  | 0.24 |      | 0.653 | 1.30  |      | 0                   |
|     | 3. VI   | 0.32  | 0.55 | 0.47 |       |       |      | 100                 |
| 2   | 25. V   | 0.07  | 0.06 | 0.09 |       |       |      | 0                   |
|     | 1. VII  | 0.35  | 0.48 | 0.47 |       |       |      | 200                 |
| 3   | 18. III | 0.13  | 0.21 | 0.25 | 0.36  | 0.65  | 0.67 | 0                   |
|     | 11. IV  | 0.25  | 0.29 | 0.27 |       |       |      | 100                 |
| 4   | 30. I   | 0.015   | 0.07 | 0.08 | 0.205 | 1.45  | 1.00 | 0                   |
|     | 2. III  | 0.03  | 0.08 | 0.09 |       |       |      | 200                 |
|     | 23. III | 0.07  | 0.07 | 0.10 |       |       |      | 390                 |
| 5   | 12. II  | 0.03  | 0.13 | 0.14 | 0.484 | 0.933 |      | 0                   |
|     | 25. IV  | 0.05  | 0.06 | 0.06 |       |       |      | 100                 |
|     | 21. V   | 0.04  | 0.07 | 0.06 |       |       |      | 200                 |
| 6   | 15. III | 0.07  | 0.07 | 0.11 | 0.233 | 1.17  | 1.20 | 0                   |
|     | 11. IV  | 0.01  | 0.02 | 0.02 |       |       |      | 100                 |
|     | 30. IV  | 0.07  | 0.09 | 0.13 |       |       |      | 150                 |

tain that in iron deficiency with anemia we may find reduced salivary secretion, and a similar phenomenon might therefore also be expected in iron deficiency without anemia. It seems highly improbable, however, that iron deficiency should be the cause of all cases of «idiopathic» xerostomia, since the hemoglobin percentage is always normal, the serum iron normal in most cases, and the typical dysphagia absent; but of course, the possibility cannot be excluded where the serum iron is low.

It may be said in effect that the same applies to the ariboflavinosis, as it is described by Geill and Lundh (1941). Their description of the patients who were improved by riboflavin coincides rather closely with the present description of the xerostomia. Hence we have, in the last 10 of our cases, looked for vascularization in cornea, which in typical form is a definite indication of ariboflavinosis. Vascularization was found in only 2 cases out of these 10. In one, the vascularization represented another eye disease, in the other it

was undoubtedly a case of ariboflavinosis. The latter patient was treated at the eye clinic with riboflavin with splendid results. We have also tried this treatment on some of the other patients, but in most instances the result has been disappointing. In all, 8 patients were treated with riboflavin, 100 to 400 mg intramuscularly in doses of 10 mg every second day. Of these patients, 2 were cured after 100 mg, 1 somewhat improved after 200 mg, but the other patients proved refractory to this treatment. The results are shown in table 3. The author also had the opportunity of observing a case of pellagra with xerostomia in a patient with anorexia nervosa where the xerostomia disappeared under treatment with riboflavin, though other B-vitamin therapy was applied at the same time. Typical cornea changes were not found in this case either.

It is far more probable that the patients who do not show any definite signs of iron deficiency or ariboflavinosis belong to the class of cases which the ophthalmologist Sjögren has described under the name of keratoconjunctivitis sicca. In his doctoral thesis Sjögren has collected a series of patients with reduced lacrymal secretion and characteristic changes in conjunctiva and cornea attributable to the lowered lacrymal secretion. 9 of his 19 cases also showed decreased salivary secretion. Anemia was not observed in any case. A histological investigation of the lacrymal glands showed either a lymphocytic infiltration or a cirrhosis of the gland. Similar conditions were found in the salivary and laryngeal glands. There can hardly be any doubt that this is the disease from which the majority of our patients suffer, even though it hardly applies to all of them.

The etiology of this disease is still unknown. Sjögren is of the opinion that it is a question of a primary glandular affection, perhaps an infection, but the histological changes can best be explained on the basis of a canalicular ascending infection made possible by the decreased secretion. This is in agreement with the circumstance that our patients seemed rather exposed to canalicular pyogenic infections of the salivary glands. Of our patients, 2 had complications of this kind, one prior to the first examination, the other in connection with a hemiplegia. Similar observations have been made in the surgical ward, purulent parotitis occurring almost exclusively post-operatively in dehydrated patients with the salivary secretion reduced as a result of the dehyd-

ration. A similar parotitis may be observed in infants, here presumably on account of a low salivary secretion [Kallmann (1937)].

E. and T. Dalsgaard-Nielsen emphasize that a primary disease in the central nervous system is the cause. This is supported by the histological investigations of Eskelund and Neel who in one patient found glious processes in the cerebrum. That an abrogated naso-ocular reflex with wanting lacrymal secretion should be interpreted as a sign of a disease in the vegetative nervous system seems somewhat improbable especially when considering that in these cases we frequently find the lacrymal glands substituted by connective tissue.

We have mentioned the appearance of a pronounced xerostomia and, in a few instances, keratoconjunctivitis sicca during pernicious anemia, sideropenic anemia, and, as a rule to a lighter degree, during ariboflavinosis. These causes, though, are hardly capable of explaining all the cases described.

One thing, however, is rather striking, viz., the enormous sex specificity of the disease, especially when eliminating all the cases where the etiology is known. The author's material comprises 21 women and 2 men who do not suffer from anemia and of whom it is not known whether they have ariboflavinosis. Sjögren's material consists of 19 women, and Dalsgaard-Nielsen's of 9 women. It is striking, moreover, how many of these women became ill at the time of the climacteric. In the author's material this is true of 4, and of the rest, only 4 became ill before, 1 of these in connection with childbirth. It was natural then in some of these cases to consider the possibility of a hormonal cause, especially associated with the function of the ovary. Unfortunately, the behavior of the salivary glands at changes in the functions of the endocrine organs is practically unknown, so that we are unable to present any experimental support. But a few other clinical observations seem to point in the same direction. Thus Sjögren emphasizes that most of his patients, in accordance with what is previously described in the literature, suffered from a polyarthritis which started or became worse in the climacteric. It is moreover striking how many of our patients suffered from endocrine complaints. Thus 2 had myxedema and 4 diabetes, though it cannot be excluded that pancreas, for example, may play a part in the process. The reduced salivary secretion in diabetes has previously been described by Fabian (1938).

That the condition of the salivary glands may change during the function of the ovaries is known from various phenomena. Thus a syndrom has been described which manifests itself by a recurring swelling of the salivary glands in the days before menses, as a rule in women with hypophoria, histologically characterized by edema of the glands and with ample secretion, even though some of the patients are dry in the mouth during the intervals [Racine (1939), Ullmann (1928)]. A few of these patients were cured by administration of corpus luteum hormone in the time before menses. We shall finally mention the sialorrhoea which is often observed during pregnancy.

Thus we are unable to say anything definite, but this possibility of an etiologic explanation of the idiopathic xerostomia should undoubtedly be considered no less important than, for example, the ariboflavinosis.

### *Consequences of Xerostomia.*

We shall finally mention the mouth symptoms which appear in consequence of a reduced salivary secretion.

As mentioned, a large number of our patients had an atrophy of the mucous membrane of the tongue. It might therefore be of interest to compare these conditions with the findings of Sjögren in the conjunctival mucous membrane in similar cases. Sjögren's description of the histological changes in conjunctiva, with a narrowing down of the epithelium and a slightly increased infiltration of lymphocytes and plasma cells into the connective tissues, comes very close to the description which Wallgren (1928) has given of the changes in the pernicious anemia glossitis. He finds an almost complete lack of secondary papillae, while the papillae of the connective tissue are but a little smaller than normal and do not extend up above the epithelium. The latter is thinner than normal, and lacks most of the cornified layer. In the subepithelial connective tissue an increased amount of lymphocytes is frequently seen. There is thus good agreement of the histological changes, which confirms the clinical observation that the salivary secretion is reduced in nearly all cases where atrophy of the tongue is observed. It is particularly in the older persons that the tongue becomes completely smooth, which corresponds to the finding of Wallgren that the papillae of the connective tissue of the tongue in older normal

persons are lower than in younger persons. The question is also elucidated by the above mentioned case of a 13-year old boy with xerostomia. Here the tongue was sometimes completely coated, sometimes fiery red and shining, but with the papillae preserved — somewhat resembling a scarlatina tongue. That the papillae of the connective tissue are preserved, even in case of the smooth tongue in pernicious anemia is also shown nicely in the photographs obtained by Henning (1936) according to the principles of cornea-microscopy. Only in 3 cases the author has seen a smooth tongue without reduced salivary secretion, when the secretion was measured by collection of the saliva. One of these was a case of sideropenic anemia, and another of recurring ulcerous glossitis. The third case was doubtful — perhaps it was one of Hunter's glossitis without changes in the peripheral blood, and with non-characteristic changes in the bone marrow.

Another symptom which is common in these patients is the glos-sodynia. This must undoubtedly be attributed to the reduced salivary secretion, since several patients, during the collection of the saliva where the mouth was very dry, complained of an aggravation of the pains, so strong that on one occasion it was necessary to interrupt the examination for this reason.

The third interesting phenomenon in these patients is the frequent appearance of bilateral fissures in the corners of the mouth. It is generally stated that patients with this symptom have increased, or at any rate normal, salivary secretion. This does not agree with the author's experience, however. All our patients with fissures in the corners of the mouth have had a reduced salivary secretion, and this symptom has also been found in all types of xerostomia, both in simple diseases of the salivary glands, and in idiopathic xerostomia. It is therefore necessary in all of these cases to consider the fissures as a simple consequence of the reduced salivary secretion, although undoubtedly in most cases it requires a poorly fitting, especially too low, prothesis as contributing factor.

## Summary.

On the basis of 49 patients with reduced salivary secretion the paper renders an account of the causes of xerostomia. Only in about one-third of the cases it is easy to diagnose the cause of the reduced secretion. These cases comprise congenital aplasia of the parotid glands, as well as inflammatory conditions of different kinds. X-ray treatment is also mentioned as a cause of decreased salivary secretion.

In the other cases it is only possible to determine the cause of the xerostomia in one-half of them. It is here a question of pernicious anemia, sideropenic anemia, and ariboflavinosis. In some the cause undoubtedly is a chronical inflammation which maintains a previously arisen xerostomia. In the rest of the cases no cause can be given, but the paper discusses the possibility of a reduction dependent on the endocrine organs, especially at the time of the climacteric.

In a rather large number of cases, fissures in the corners of the mouth, atrophy of the mucous membrane of the tongue, and pains in the tongue are found to be consequences of the reduced salivary secretion.

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Aus der 1. Medizinischen Abteilung des Sahlgrenschen Krankenhauses,  
Göteborg (Schweden). (Vorstand: Prof. Dr. med. Gotthard Söderbergh.)

## **Die Behandlung der Raynaudschen Krankheit mit 2-Benzyl-4,5-Imidazolin (Priscol Ciba).<sup>1</sup>**

Von

**TORSTEN LINDQVIST.**

(Bei der Redaktion am 1. Oktober 1942 eingegangen).

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### **Einleitung.**

Die Therapie der Raynaudschen Krankheit hat lange ausserordentlich grosse Schwierigkeiten bereitet. Die empfohlenen Präparate sind in der Regel wirkungslos gewesen. Die Sympathektomie hat bei einem Teil der Fälle eine bedeutende Linderung bringen können, musste aber auf Grund ihres in technischer Beziehung schwierigen Charakters für die schwereren Fälle reserviert werden. Die Indikationen für eine Operation mussten ausserdem weiterhin eingeschränkt werden, da die Beschwerden oft auch nach technisch geglückten Operationen wieder auftraten.

Es ist daher interessant zu erfahren, dass mehrere Untersucher über sehr gute Resultate bei der Behandlung von Raynaudscher Krankheit mit Hilfe eines neuen Mittels berichten, welches von »Ciba« unter dem Namen Priscol in den Handel gebracht wird. Dieses Mittel mit der chemischen Zusammensetzung 2-Benzyl 4,5-Imidazolinhydrochlorid, wurde von Hartmann und Isler (1) synthetisch dargestellt. Über günstige klinische Erfahrungen mit diesem Präparat bei der Behandlung der Raynaudschen Krankheit berich-

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<sup>1</sup> Ein präliminärer Bericht über diese Untersuchungen wurde vor der Versammlung der Schwedischen Neurologen-Vereinigung in Stockholm am 8. Mai 1942 erstattet.



ten Kohlmeyer (2), Brack (3), Singer (4), Weitzmann (5), Schnetz und Fluch (6) sowie Ekbom und Fogstrand (7). Bei experimentellen Untersuchungen an Kaninchen und Hunden haben Meier und Müller (8) eine bedeutende Erweiterung der Hautgefässe mit besserer Durchblutung nach sowohl peroraler wie auch intravenöser und intramuskulärer Verabreichung von Priscol nachweisen können, und Schnetz und Fluch (6) haben einen gleichartigen Effekt bei Kröten festgestellt. Zothe (9) hat bei Versuchen am Menschen eine Erhöhung der Strömungsgeschwindigkeit des Blutes in den unteren Extremitäten nach Zuführung von Priscol registrieren können, woraus er auf eine verbesserte periphere Durchblutung schliesst. Diese experimentellen Untersuchungen geben also eine gute Erklärung für die günstigen Resultate, die die klinische Prüfung des Präparates annehmen lässt.

Man hat es jedoch oft bei klinischen Untersuchungen erleben müssen, dass Präparate, die für die ersten Untersucher gute Resultate ergaben, sich bei der Nachprüfung als von zweifelhaftem Wert darstellten oder als wertlos erwiesen und bald in Vergessenheit gerieten. Auch bei einem kritischen Studium der hier genannten Veröffentlichungen über die klinische Prüfung von Priscol kann man sich gewisser Zweifel über den Wert des Präparates nicht erwehren. Die Zahl der vorgelegten Fälle ist in der Regel zu klein, um ein Urteil zu gestatten. So hat Kohlmeyer (2) 2 Fälle behandelt, bei dem Material von Brack (3) dürften 2 Fälle als Raynaudsche Krankheit bezeichnet werden können, und Singer (4) berichtet über 2 Fälle, von denen nur der eine ein Fall von Raynaud zu sein scheint, der andere eine einfache Akrozyanose. Bei den grösseren Patienten-Serien, über die Weitzmann (5) sowie Schnetz und Fluch (6) berichten, ist es ganz unklar, ob Fälle mit der wirklichen Raynaudschen Krankheit dabei waren. Die Fälle, welche ausführlicher unter diesem Namen beschrieben werden, sind offenbar entweder vasomotorische Störungen anderer Art oder auch obturierende Gefässkrankheiten. Nur Ekbom und Fogstrand (7) haben ein grösseres einheitliches Material von 16 Fällen, alle mit intermittierenden arteriellen Spasmen, so dass ihren Ergebnissen bezüglich Besserung auf Grund von Priscolbehandlung bei allen Fällen grösserer Wert zuerkannt werden muss.

Bei klinischen Beobachtungen über den Effekt einer Therapie muss man ja unbedingt ein grosses Material haben, möglichst von

verschiedenen Untersuchern, wenn man sich ein richtiges Bild von der Wirkung der Behandlung machen will. Es erscheint mir daher angebracht, auch über meine Beobachtungen zu berichten, zumal die Untersuchungen ausgeführt wurden, ehe Ekholm und Fogstrand ihre Resultate dargelegt haben.

Wenn es sich darum handelt, den Erfolg einer Behandlung nur auf Grund der Angaben der Patienten über eine eventuelle Besserung zu beurteilen, hat man immer das Gefühl, dass die Suggestion bei den Patienten oder dem Untersucher eine Rolle spielen und das Bild trüben kann. Das Sicherheitsgefühl wächst im gleichen Masse, in dem man in der Lage ist, den Effekt objektiv zu messen. Bei den von mir behandelten Fällen habe ich daher soweit irgend möglich versucht, eine Registrierung des Priscoeffektes an den Fingern der Patienten zu erhalten, und zwar durch Messung der bei Verabreichung von Prisco auftretenden Hauttemperatur-Veränderungen an den Fingerspitzen.

Es zeigte sich bei diesen Untersuchungen, dass die Frage der geeignetsten Versuchsbedingungen von grösstem Interesse war. Eine ganz grosse Anzahl Arbeiten der letzten Jahre hat sich mit der Frage des vasodilatierenden Effekts verschiedener Mittel beschäftigt, aber in keiner dieser Arbeiten findet man Näheres über die Frage der geeignetsten Untersuchungsbedingungen. Es zeigte sich bald bei meinen Untersuchungen, dass es zur Vermeidung fehlerhafter Ergebnisse von grösster Wichtigkeit war, unter bestimmten Bedingungen zu arbeiten. Ein grosser Teil meiner Arbeit wurde daher der Frage der geeignetsten Methodik bei der Untersuchung des Effektes vasodilatierender Mittel gewidmet.

#### Die Versuchsanordnung bei den Hauttemperaturmessungen.

Für die Messungen der Hauttemperatur wurde ein Tykos «Dermatherm» (Kupfer-Konstantanelement) verwandt, das die Ablesung der Hauttemperatur mit einer Genauigkeit von  $0.1^{\circ}$  gestattet (alle Temperaturangaben in Celsiusgraden). Die Zimmertemperatur wurde an einem schnellreagierenden (kontrollierten) Quecksilberthermometer abgelesen.

Vor Beginn einer jeden Untersuchung hatten die Patienten eine Zeit lang in einem  $17-18^{\circ}$  warmen Zimmer zu ruhen, so dass die Hände sich warm anfühlten.

In der Regel folgten die Untersuchungen folgendem Schema:

Bei der ersten Untersuchung wurde der Patient in ein Zimmer mit einer Temperatur von  $14-15^{\circ}$  verbracht. Die Kleidung war dieselbe, die der

Patient gewöhnlich im Hause trug. Die Hände wurden 10 Minuten lang in 15° warmes Wasser gehalten, dann herausgenommen und vom Untersucher abgetrocknet, ohne dabei gerieben zu werden. Dann wurden die Temperaturen der Volarseite der Endphalanx gemessen, im allgemeinen an allen Fingern, in einigen Untersuchungsreihen nur an den Daumen und kleinen Fingern. Bei dieser Methode hielt sich die Hauttemperatur der Finger in der Regel so gut wie konstant während der Zeit, die die Messungen in Anspruch nahmen, oft eine Stunde oder mehr. In einigen Fällen kam es jedoch vor, dass die Fingertemperatur einige Zeit nach Herausnahme der Finger aus dem Wasser zu steigen begann; manchmal ziemlich rasch. Bei diesen Fällen wurde der Versuch ein bis zwei Tage später wiederholt, wobei der Patient jedoch leichter gekleidet war. Teilweise genügte es schon, dass der Patient Kleid bzw. Anzug auszog, bei manchen Fällen musste der Untersuchte auch Schuhe oder Strümpfe ausziehen, um zu erreichen, dass die Fingertemperatur sich während der genannten Versuchsbedingungen konstant hielt.

Bei den nachfolgenden Untersuchungen war jeder Patient genau so gekleidet wie bei der Untersuchung, bei welcher es geglückt war, eine konstant niedrige Fingertemperatur zu erhalten (= Kontrollversuch). Die Zimmertemperatur wurde auf gleichem Niveau gehalten wie beim Kontrollversuch. Das Eintauchen der Hände in 15° warmes Wasser, das Abtrocknen und die Messung der Hauttemperatur an den Fingerspitzen wurde auf gleiche Weise vorgenommen. Vor oder während den Messungen erhielt der Patient Priscol peroral oder intramuskulär in Quantitäten, die bei jedem Fall besonders angegeben werden. Ein und derselbe Patient wurde stets zu etwa derselben Tageszeit gemessen und zwischen den verschiedenen Untersuchungen lagen immer wenigstens 24 Stunden.

Eine Motivierung für die angewandte Methodik wird später in der Diskussion gegeben.

### Kasuistik.

Da die Messungstabellen der Fingerhauttemperaturen ziemlich viel Platz in Anspruch nehmen, werden die Resultate der Messungen nur in kurzen Zusammenfassungen für die verschiedenen Untersuchungen angegeben.

#### *Fall 1) ♀. E. J., 31jährige Frau.*

Hat stets Beschwerden wegen kalter Hände und Füße gehabt. Im November 1941 begann sie darüber zu klagen, dass die Finger weiss wurden, auch bei Zimmertemperatur. Wenn die Finger weiss wurden, bekam sie gleichzeitig Schmerzen in denselben. Sie wachte oft nachts wegen der Schmerzen in den Fingern auf.

Bei der Untersuchung am 16. 12. 1941 hatten die Hände normales Aussehen im warmen Zimmer. Als sie in ein Zimmer mit einer Temperatur von 16° verbracht wurde, wurden die Finger nach einer Weile bläulich blass

und sie klagte über Prickeln in den Fingern. Als sie in diese Temperatur verbracht worden war, hatte sie eine Fingertemperatur von ca.  $25^{\circ}$  gehabt. Diese sank während der folgenden 7 Minuten ca.  $1.5^{\circ}$ . Nach Ablauf dieser Zeit bekam sie 0.02 g Priscol intramuskulär. Schon nach 3 Minuten begann die Hauttemperatur zu steigen, und 10 Minuten nach der Injektion war sie — je nach Finger — auf  $30\text{--}33^{\circ}$  gestiegen.

Es wurde ihr nun Priscol, 3 mal täglich 1 Tablette zu 0.025 g verordnet. Alle ihre Beschwerden verschwanden unmittelbar nachdem sie diese Behandlung begonnen hatte, sie hatte rote warme Hände und keine Schmerzen, so dass sie nachts gut schlief. Eine Woche nach Beginn der Behandlung trat jedoch eine ausgesprochene urticarielle Dermatitis an beiden Händen und Unterarmen auf, so dass die Behandlung abgebrochen werden musste. Da sie nun ihre Tabletten nicht mehr einnahm, begann sie wieder Kältebeschwerden in den Füßen zu bekommen, aber in geringerem Umfang als früher. Während des ganzen langen ungewöhnlich kalten Winters 1942 hatte sie dagegen keinerlei Beschwerden an den Händen, und dies ist immer noch der Fall, im Juli 1942.

**Fall 2) ♀. E. R., 19jährige Kontoristin.**

War stets etwas verfroren gewesen. Die Finger wurden in der Kälte leicht weiss, und wenn sie wieder ins Warme kam, dauerte es sehr lange, bis die Finger warm wurden. Im November 1941 begann sie Schwierigkeiten bei der Arbeit zu bekommen. Sie musste sich in einem Zimmer mit einer Temperatur von etwa  $14^{\circ}$  aufhalten, wobei die Hände weiss und steif wurden.

Wenn man bei der Untersuchung ihre Hände in  $15^{\circ}$  warmem Wasser abkühlte, wurden die Finger weiss. Bei langsamer Erwärmung wurden sie erst ausgesprochen zyanotisch, dann blau mit roten Flecken und schliesslich rot. Wenn sie nach Abkühlung der Hände die Füße in  $44^{\circ}$  warmes Wasser stellte, dauerte es fast eine halbe Stunde, bis die Temperatur der Fingerspitzen zu steigen begann, aber alsdann erfolgte eine sehr rasche Steigerung.

Die experimentellen Untersuchungen ergaben folgendes Resultat. Beim Kontrollversuch war die Fingerspitzentemperatur unmittelbar nach Herausnahme der Hände aus dem Wasser ca.  $16^{\circ}$ , sank dann langsam auf ca.  $15^{\circ}$  und stieg dann, 45 Minuten nach Herausnahme aus dem Wasser, wieder langsam auf  $16\text{--}16.5^{\circ}$ . Beim nächsten Versuch bekam sie 0.02 g Priscol intramuskulär, 6 Minuten nachdem sie die Hände aus dem Wasser genommen hatte. 4 Minuten nach der Injektion begannen die vorher (und während des ganzen Kontrollversuches) bläulichweissen Finger und Hände hellrot zu werden, und die Fingerspitzentemperatur begann zu steigen, jedoch in verschiedenem Tempo an den verschiedenen Fingern. So war 16 Minuten nach der Injektion die Temperatur der meisten Finger ungefähr  $21^{\circ}$ , aber der rechte Daumen hatte  $18^{\circ}$  und der linke Daumen  $19^{\circ}$ . Die Fingertemperatur hielt sich dann während annähernd einer Stunde konstant, wenn auch mit einer unbedeutenden Abkühlungstendenz. Ein weiterer Injektionsversuch gab praktisch gesehen genau dasselbe Resultat. Bei

einem anderen Versuch bekam sie zwei Tabletten Priscol zu je 0.025 g, 25 Minuten bevor die Hände in das 15gradige Wasser getaucht wurden und 35 Minuten bevor die Messungen begannen. Als die Hände aus dem Wasser genommen wurden, waren sie  $0.5-1^{\circ}$  wärmer als beim Kontrollversuch und den anderen Versuchen, während derer sie nicht unter Priscoleinwirkung gestanden hatte, aber sie waren bleich mit zyanotischem Einschlag. 7 Minuten nach Herausnahme der Finger aus dem Wasser begannen sie eine warme hellrote Farbe anzunehmen, und die Fingerspitzentemperatur fing langsam zu steigen an, so dass sie 50 Minuten nach Beginn der Messungen im Durchschnitt  $20^{\circ}$  betrug, also  $3.5-4^{\circ}$  mehr als beim Kontrollversuch.

Mitte Dezember 1941 begann die Priscolbehandlung mit 3 mal täglich einer Tablette zu 0.025 g. Alle Beschwerden verschwanden. Die Finger blieben rot und warm in der gleichen Zimmertemperatur, bei der sie früher wegen ihrer Beschwerden in den Händen nur mit grösster Schwierigkeit hatte arbeiten können. Bei diesem Fall war es besonders interessant, die Veränderung des Gesamtaussehens der Patientin zu beobachten, die während der Priscolbehandlung eintrat. Sie hatte früher verfroren ausgesehen und hatte eine bläulich blasse und kalte Gesichtsfarbe. Infolge der Behandlung bekam sie eine warme Gesichtsfarbe, mehr Glanz in den Augen und das Gesicht wirkte etwas voller, was alles ausserordentlich vorteilhaft für ihr Aussehen wirkte. Auch ihr Bräutigam sprach seine grosse Zufriedenheit mit dem Resultat aus. Sie nahm die Tabletten in gleicher Dosis während des ganzen Winters 1941/42 und war beschwerdefrei, solange sie die Tabletten nahm. Wiederholte Male wurde der Versuch gemacht mit den Tabletten aufzuhören, aber da traten die Beschwerden wieder auf, meist schon innerhalb von 24 Stunden. So allmählich konnte sie die Dosis jedoch etwas vermindern.

*Fall 3) ♀. E. N. 30jährige Schulküchenlehrerin.*

Seit ihrer Kindheit wurde sie leicht kalt an Händen und Füssen. In der Kälte wurden die Finger weiss, namentlich wenn sie die Hände in kaltem Wasser gehabt hatte, was bei ihrem Beruf störend ist. Wenn sie aus der Kälte in die Wärme kommt, werden die Hände blau, und es kann bis zu einer Stunde dauern, ehe ihre Hände wieder warm werden.

Wenn man ihre Hände in  $15^{\circ}$  warmem Wasser abkühlte, wurden die Finger weiss und beim Wiedererwärmen wurden sie zyanotisch, ehe sie eine wärmere Farbe annahmen. Die Fingerspitzentemperatur betrug beim Kontrollversuch  $16-16.5^{\circ}$ . Nach intramuskulärer Injektion von 0.02 g Priscol begannen die Finger nach 6 Minuten heller zu werden, und gleichzeitig begann die Hauttemperatur der Fingerspitzen rasch anzusteigen, so dass die Temperatur an den Fingerspitzen 12 Minuten nach der Injektion sich zwischen  $29.3^{\circ}$  und  $31.6^{\circ}$  bewegte, also eine Steigerung von im Durchschnitt ungefähr  $2^{\circ}$  Minute aufwies. Am linken kleinen Finger stieg die Temperatur in einer Minute mit  $5.5^{\circ}$ . 28 Minuten nach der Injektion wurden die Finger wieder für 10 Minuten in  $15^{\circ}$  warmes Wasser getaucht. Die Fingerspitzentemperatur sank da auf etwa  $17^{\circ}$ , begann dann aber wieder

anzusteigen, so dass sie 20 Minuten nach dieser zweiten Abkühlung sich zwischen 22 und 25° bewegte.

Ab Anfang Januar 1942 bekam sie 3 mal täglich eine Tablette Priscol zu 0.025 g und wurde vollkommen beschwerdefrei. Sie konnte ohne Unannehmlichkeit mit den Händen in kaltem Wasser sein. Nachdem sie 120 Tabletten genommen hatte, hörte sie auf damit, ohne dass die Beschwerden wiederkämen, und trotz des ungewöhnlich strengen Winters war sie auch weiterhin beschwerdefrei. Ende Juni 1942 sind die Beschwerden noch nicht wieder aufgetreten.

**Fall 4) ♂. K. O. B. 25jähriger Strassenbahnarbeiter.**

Hat stets kalte Hände gehabt. In den letzten Jahren wurden die Finger in der Kälte weiss, und wenn er wieder ins Warme kam, dauerte es lange, bis die Hände warm wurden. In der letzten Zeit bekam er auch Schmerzen in den Fingern, wenn sie weiss wurden. Gegen Ende 1941 wurden diese Beschwerden so ausgesprochen, dass er seiner Arbeit nicht mehr nachkommen konnte, da er im Freien bei starker Kälte zu arbeiten hatte.

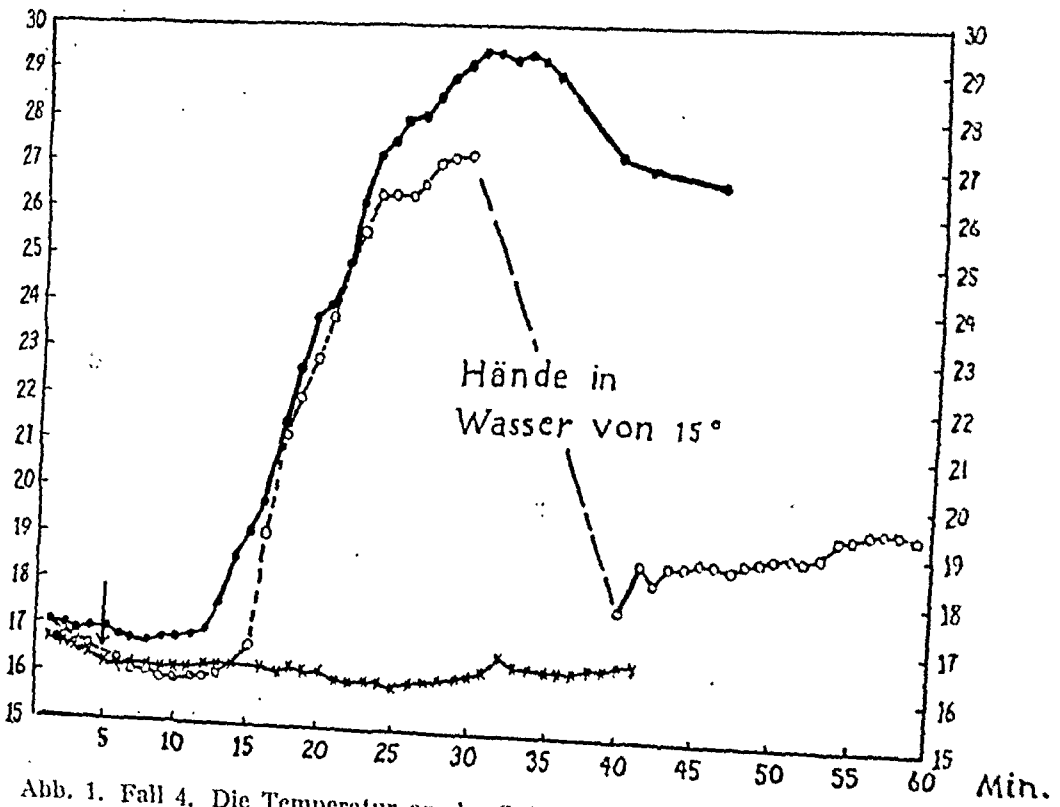


Abb. 1. Fall 4. Die Temperatur an der Spitze des rechten kleinen Fingers.

x-x-x-x-x = Kontrollversuch

-o-o-o-o-o- = Injektionsversuch. Bei ↓ intramuskuläre Injektion von 0.02 g Priscol.

--- = Tablettenversuch. 20 Minuten vor Beginn der Messungen, 0.05 g Priscol per os.

Zimmertemperatur bei allen Versuchen 14—15°.

Wenn er die Hände in 15° warmes Wasser gehalten hat, sind die Finger weiss und die Hände etwas zyanotisch. Bei langsamer Erwärmung werden Finger und Hände erst zyanotisch, dann blau mit roten Flecken, schliesslich rot. Messungen der Hauttemperatur an den Fingerspitzen bei Erwärmung des Körpers durch Eintauchen der Füsse in 44° warmes Wasser zeigen, dass nach einer langen Latenzzeit eine schnelle Erweiterung der Fingergefässe eintritt, vielleicht mit Ausnahme des rechten Daumens, bei dem die Erweiterung etwas langsamer vor sich geht.

Die Resultate der experimentellen Untersuchungen bei diesem Fall gehen aus den Kurven der Abb. 1 hervor, die sich auf den rechten kleinen Finger beziehen. Die anderen Finger wiesen im Prinzip die gleichen Verhältnisse auf, doch waren die Temperaturveränderungen unter Priscoleinwirkung am rechten Daumen weniger ausgesprochen.

Er bekam ab Mitte Januar 1942 3 mal täglich 1 Priscoltablette zu 0.025. Abgesehen von einem leichten Frostgefühl kurz nach Einnahme der Tablette hatte er keine Unannehmlichkeiten durch die Medikation. Die Beschwerden hörten fast unmittelbar auf, und nach einer Woche nahm er seine Arbeit wieder auf. Nachdem er eine Verpackung mit 40 Tabletten genommen hatte, hörte er mit der Medikation auf, ohne dass die Beschwerden wieder auftraten, und er konnte seine Arbeit im Freien während des strengen Winters 1942 ausführen ohne Beschwerden zu haben. Noch Ende Juli 1942 war er ganz beschwerdefrei.

#### **Fall 5) ♀. A. H., 35jährige Kassiererin.**

Als Kind soll sie sich die Hände erfroren haben und sie hatte mehrere Jahre lang Frostwunden an den Fingern. Seitdem hat sie immer leicht kalte Hände bekommen. Im letzten Jahre bekam sie weisse Finger in der Kälte und die Hände wurden steif bei Abkühlung. Gegen Ende 1941 musste sie in einem ziemlich kalten Zimmer arbeiten und konnte da nur mit Schwierigkeit ihrer Arbeit nachkommen.

Nach Eintauchen der Hände in 15° warmes Wasser werden die Finger ganz weiss, bei langsamer Erwärmung erst zyanotisch, dann blau mit roten Flecken. Messung der Fingerhauttemperatur bei Erhöhung der Körpertemperatur zeigt das Vorkommen einer rein spastischen Gefässaffektion ohne Zeichen von Gefässverschluss. — B. M. B. + 27 %.

Als man sie in ihrer gewöhnlichen Kleidung in ein 17° warmes Zimmer setzte, bekam sie bald blaue und kalte Finger und die Temperatur der Fingerspitzen sank innerhalb 10 Minuten im Durchschnitt 3°. Dann erhält sie 0.02 g Priscol intramuskulär. Während der folgenden 6 Minuten sinkt die Fingertemperatur weiter, aber dann beginnt ein langsamer Anstieg von 2—2.5° im Verlauf von 10 Minuten, woraufhin die Temperatur sich weitere 10 Minuten konstant hält. — Nach intramuskulärer Injektion von 0.015 g Priscol unter den üblichen Versuchsbedingungen beginnt die Temperatur etwa 5 Minuten nach der Injektion langsam zu steigen, so dass sie 25 Minuten nach der Injektion 3—3.5° gestiegen ist und sich auf dieser Höhe etwa weitere 20 Minuten konstant hält.

Ab Anfang Dezember 1941 erhielt sie 3 mal täglich 1 Tablette Priscol zu 0.025 g. Dabei gingen ihre Beschwerden etwas zurück, aber sie war nicht beschwerdefrei. Die Dosis wurde dann auf 2 mal 3 Tabletten erhöht, woraufhin die Beschwerden weiterhin zurückgingen, ohne aber ganz zu verschwinden. Als sie dann ausserdem noch die Hände mit Priscolsalbe einschmierte, wurde ihr Zustand sehr erträglich, aber auch dann war sie nicht frei von Beschwerden. Irgendwelche Nebenwirkungen infolge der grossen Dosis Priscol traten nie bei ihr auf. Wiederholt machte sie den Versuch, die Behandlung abzuschliessen oder die Dosis zu verringern, aber da traten die Beschwerden stets wieder innerhalb von 24 Stunden auf.

**Fall 6)** ♀. E. M., 21jährige Angestellte in einem Milchladen.

Leidet seit Jahren unter kalten Händen. Die Finger werden weiss und steif in der Kälte, was sie bei der Arbeit stört, da sie als Angestellte in einem Milchladen sich häufig in kaltem Lokal aufhalten muss. Ausserdem werden die Hände oft stark zyanotisch.

Bei Abkühlung in 15° warmem Wasser werden die Finger weiss und bei langsamer Erwärmung erst zyanotisch und dann rotfleckig. Eine Injektion von 0.02 g Priscol intramuskulär nach der üblichen vorhergegangenen Abkühlung erzeugt einen Anstieg der Fingerspitzen-Hauttemperatur, die schon 2—3 Minuten nach der Injektion einsetzt. 5 Minuten nach der Injektion sind Hände und Finger hellrot. 10 Minuten nach der Injektion ist die Temperatur 4—8.5° gestiegen — recht verschieden an den verschiedenen Fingern — und hält sich alsdann im grossen und ganzen konstant während der folgenden 10 Minuten. Nachdem die Hände 20 Minuten nach der Injektion aufs neue in 15° warmes Wasser verbracht worden und 10 Minuten darin verblieben waren, sind die Fingerspitzen wieder auf die Temperatur von vor der Injektion heruntergegangen, und die Temperatur steigt dann nur langsam wieder an; etwa 2° in 20 Minuten. — Bei einer anderen Untersuchung bekam sie 20 Minuten vor Beginn der Abkühlung 2 Tabletten Priscol zu 0.025 g, aber da trat keine Steigerung der Temperatur der Fingerspitzen während 90 Minuten nach Beginn der Messungen ein.

Ab Mitte Januar 1941 erhielt sie 3 mal täglich 1 Tablette Priscol zu 0.025 g und hatte daraufhin bedeutend weniger Beschwerden an ihren Händen, ohne doch frei von Beschwerden zu sein. Da sie bei ihrer Arbeit die Hände abkühlen musste, wurde ihr empfohlen, sich eine andere Tätigkeit zu besorgen und sie bekam dann bald Anstellung in einem Bäckerladen, wo sie in dem warmen Arbeitslokal keine Beschwerden mehr hatte.

**Fall 7)** ♀. G. B., 21jährige Verkäuferin.

Hat seit ihrer Kindheit unter kalten Händen gelitten. Wenn sie kalt badet oder in die Kälte kommt, werden die Finger weiss und oft bekommt sie gleichzeitig Schmerzen in den Fingern.

Als die Hände in 15° warmem Wasser abgekühlt wurden, wurden die Finger weiss. Eine Messung der Fingerhauttemperatur bei Erwärmung der Patientin zeigte, dass spastische Gefässaffektionen ohne Zeichen für Gefässverschluss vorlagen.



Bei diesem Fall war es sehr schwer, bei den Kontrolluntersuchungen eine konstante, niedrige Temperatur der Fingerspitzen zu erzielen. Wenn sie in ihrer gewöhnlichen Kleidung auf die übliche Weise abgekühlt wurde, wurden die Finger, wie bei den anderen Patienten, nach dem Wasserbade kalt, aber schon nach 10—20 Minuten erweiterten sich die Fingerarterien, allerdings in sehr verschiedenem Ausmass und mit verschiedener Geschwindigkeit bei den verschiedenen Fingern. Bei einer Gelegenheit wurde z. B. eine längere Weile ein Temperaturunterschied von  $12^{\circ}$  zwischen rechtem Daumen und kleinem Finger festgestellt. Erst als sie ohne Kleid, Strümpfe und Schuhe in dem kalten Zimmer sass, hielt sich die Fingerspitzentemperatur bei der üblichen Abkühlung konstant niedrig. — Nachdem sie unter diesen Versuchsbedingungen 23 Minuten vor Beginn der Messungen 2 Tabletten Priscol zu 0.025 g erhalten hatte, war sie unmittelbar nach Herausnahme der Hände aus dem  $15^{\circ}$  warmen Wasser fast genau so kalt wie beim Kontrollversuch. Etwa 15 Minuten danach begann ein langsamer Anstieg der Fingerspitzentemperatur, so dass sie nach 40 Minuten im Durchschnitt  $3^{\circ}$  wärmere Fingerspitzen hatte als beim Kontrollversuch, bei dem sich die Temperatur praktisch genommen während der ganzen Zeit unverändert gehalten hatte. Eine Stunde nach Beginn der Messungen im Priscolversuch begannen die Fingerspitzen wieder kälter zu werden, und die Finger, die vorher eine warme rote Farbe angenommen hatten, wurden wieder bläulich blass.

Ab Ende Januar 1942 erhielt sie 3 mal täglich 1 Tablette Priscol zu 0.025 g. Da sie nach einigen Wochen noch keine nennenswerte Besserung verspürte, wurde die Dosis auf 3 mal täglich 2 Tabletten erhöht. Sie hatte daraufhin nicht mehr ganz so kalte Hände, aber im übrigen waren die Beschwerden unverändert. Sie hatte kein Unbehagen auf Grund der Behandlung, ausser dass sie ihr Gesicht unangenehm warm empfand und dass Brennen in der Augenbindehaut auftrat. Als sie dann neben den 2 Tabletten Priscol per os auch noch die Hände mit Priscolsalbe einschmierte, ging es ihr ganz annehmbar, aber sie war nicht frei von Beschwerden.

**Fall 8) ♀. G. J., 21jährige Kassiererin.**

Hat seit ihrer Kindheit sehr unter kalten Händen und Füssen zu leiden gehabt. In den letzten Jahren wurden die Finger in der Kälte weiss und steif, und bei anschliessender Erwärmung wurden die Hände stark blau. Im Zusammenhang mit den Menses pflegte sie einen juckenden Ausschlag an den Fingern zu bekommen, manchmal mit kleineren Ulzerationen. Auch die übrigen Beschwerden waren stärker während der Menses, die stets nur in geringem Ausmass aufgetreten waren und nur einen halben Tag dauern.

Bei Abkühlung in  $15^{\circ}$  warmem Wasser werden die Finger weiss. Bei darauf folgender Erwärmung werden sie zyanotisch mit roten Flecken. — Perniones typischen Aussehens.

Nach Injektion von 0.02 g Priscol intramuskulär unter den üblichen Versuchsbedingungen begannen die Finger schon 4 Minuten nach der Injektion eine warme rote Farbe anzunehmen. Gleichzeitig begann die Fingerspitzentemperatur zu steigen. 13 Minuten nach der Injektion variierte sie

von 18.8° am rechten Mittelfinger bis 23.4° am linken Mittelfinger gegen 15.5—16° bei Vornahme der Injektion. Gleichzeitig war die Basis des linken Mittelfingers, die vor der Injektion ein Grad wärmer als die Spitze gewesen war, 3° kälter als die Spitze. Die Fingerspitzentemperatur hielt sich alsdann während weiterer 20 Minuten im grossen und ganzen konstant, während die Basis des linken Mittelfingers allmählich die gleiche Temperatur annahm wie die Spitze. Die Hände wurden dann für 10 Minuten in 15° warmes Wasser verbracht. Beim Herausnehmen hatten sie von Anfang an eine warme rote Farbe, ohne zyanotischen Einschlag, waren aber doch genau so kalt wie beim Wasserbad vor der Injektion. Die Temperatur hielt sich dann ungefähr 20 Minuten lang konstant, woraufhin ein langsamer Anstieg begann, so dass nach weiteren 10 Minuten eine Steigerung von 2° stattgefunden hatte.

Bei einem anderen Versuch erhielt sie 20 Minuten vor Beginn der Abkühlung 2 Tabletten Priscol zu 0.025 g. Bei Herausnahme der Hände aus dem Wasser waren sie rotblau und nur wenig wärmer als beim Kontrollversuch. Nach 8 Minuten begann ein langsamer Anstieg der Fingerspitzentemperatur und nach 20 Minuten waren die Finger ganz hell geworden. 30 Minuten nach Herausnahme aus dem Wasser war die Temperatur ungefähr 2.5° gestiegen — im grossen und ganzen gleich an allen Fingern — und hielt sich dann während weiterer 30 Minuten konstant.

Ab 23. I. 1942 erhielt sie 3 mal täglich 1 Tablette Priscol zu 0.025 g, fühlte jedoch nur eine unbedeutende Besserung davon. Als sie dagegen morgens 2 Tabletten und mittags und abends je 1 Tablette einnahm, hatte sie nur unbedeutende Beschwerden an den Händen, klagte jedoch über Brennen in den Augenbindehäuten. Bei der nächsten Menstruation waren die Fingerausschläge bedeutend weniger hervortretend als früher, und es traten keine Ulzerationen auf. Da sie jedoch nicht ohne Beschwerden war, und da ihre Beschwerden einen deutlichen Zusammenhang mit den Menses hatten, die sehr spärlich waren, wurde eine Follikulinbehandlung eingeleitet, wobei sie 3 mal wöchentlich eine Injektion von 10,000 I. E. (Ovex Leo) erhielt. Während dieser Behandlung wurde sie praktisch genommen frei von Beschwerden, und die Menses wurden reichlicher.

**Fall 9) ♀. V. P., 33jährige Frau.**

Seit 5—6 Jahren leidet sie darunter, dass die Finger in der Kälte weiss werden, was immer ausgesprochener wurde, und sie hat oft gleichzeitig Schmerzen in den Fingern. Wenn sie aus der Kälte wieder ins Zimmer kommt, dauert es fast eine Stunde, bis die Hände wieder warm werden. Während dieser Zeit hat sie Schmerzen in den Händen und kann sie nicht gebrauchen.

Als sie die Hände in 15° warmes Wasser gehalten hatte, waren die Finger vollkommen weiss, und nach Erwärmung wurden sie erst zyanotisch und dann blau mit roten Flecken.

Nach intramuskulärer Injektion von 0.02 g Priscol unter den üblichen Versuchsbedingungen, begannen die Finger schon 3 Minuten nach der Injektion hell zu werden; gleichzeitig wurde ihr übel und schwindlig, so dass

sie sich einige Minuten hinlegen musste. Die Fingerspitzentemperatur stieg innerhalb 4 Minuten  $2.5\text{--}5^\circ$ , verschieden bei verschiedenen Fingern, und hielt sich dann 30 Minuten lang konstant.

Als sie 3 mal täglich 1 Tablette Priscol zu  $0.025\text{ g}$  einnahm, war sie vollkommen frei von Beschwerden. Sie bekam eher etwas zu warme Hände, hatte aber im übrigen keinerlei Unbehagen. Nachdem sie 40 Tabletten genommen hatte, hörte sie auf, woraufhin wieder Beschwerden an den Fingern in der Kälte auftraten, aber in viel geringerem Ausmass als bevor sie die Tabletten genommen hatte, und Ende Juli 1942 sind die früheren Beschwerden noch nicht wieder aufgetreten.

**Fall 10) ♀. B. J., 18jährige Bauerntochter.**

Seit einigen Jahren werden die Finger bei Abkühlung weiss und kalt und schmerzen oft gleichzeitig.

Bei Abkühlung in  $15^\circ$  warmem Wasser werden die Finger weiss; bei langsamer Erwärmung zyanotisch mit roten Flecken.

Bei einer Untersuchung bekam sie 2 Tabletten Priscol zu  $0.025\text{ g}$ . 15 Minuten später wurden die Hände in  $15^\circ$  warmes Wasser getaucht, um 10 Minuten darin zu verbleiben. Als die Hände aus dem Wasser genommen wurden, waren sie hellrot und  $2\text{--}2.5^\circ$  wärmer als beim Kontrollversuch. Nach einer leichten und kurzzeitigen Senkung der Fingerspitzentemperatur, begann eine langsam einsetzende Erwärmung, so dass sie nach 30 Minuten eine Temperatur von  $20\text{--}25^\circ$  an den Fingerspitzen hatte, also recht ver-



Abb. 2. Fall 10. Die Temperatur an der Spitze des linken kleinen Fingers.

x-x-x-x-x = Kontrollversuch  
 •-•-•-•-• = Tablettenversuch. 25 Minuten vor Beginn der Messungen  
 $0.05\text{ g}$  Priscol per os.  
 Zimmertemperatur bei beiden Versuchen  $15\text{--}16^\circ$ .

schieden an den verschiedenen Fingern. Danach trat eine geringere Temperatursenkung ein. Die Temperaturverhältnisse am linken kleinen Finger werden durch Abb. 2 veranschaulicht. Bei diesem Fall erfolgte die Temperatursteigerung an den Fingerbasen — gemessen an den beiden Mittelfingern — vor der an den Fingerspitzen, während die Handflächen während der ganzen Zeit etwas wärmer waren als die Finger.

Als sie 3 mal täglich 1 Tablette Priscol zu 0.025 g einnahm, fühlte sie sich bedeutend wärmer an den Fingern und war im grossen und ganzen frei von Beschwerden.

**Fall 11) ♀. J. M., 55jährige Krankenhausangestellte.**

Seit vielen Jahren hat sie darunter gelitten, dass die Finger kalt und weiss werden, manchmal ohne bekannten äusseren Grund, manchmal bei Kälte. Gleichzeitig bekommt sie Schmeizen in den Fingern. Wenn sie ihre Hände der Kälte aussetzt, schwellen sie an; oft hochgradig. In der letzten Zeit haben sich die Beschwerden vergrössert, da sie eine Beschäftigung bekommen hat, bei der die Hände viel in kaltem Wasser sind. Sie musste deshalb krankgeschrieben werden.

Wenn sie auf die übliche Weise die Hände in 15° warmes Wasser hält, werden die Finger weiss. Wenn man die Hände langsam erwärmt, werden sie zyanotisch. Allmählich tritt eine bedeutende Weichteilschwellung der Finger auf, und ungefähr 45 Minuten nachdem sie die Hände aus dem

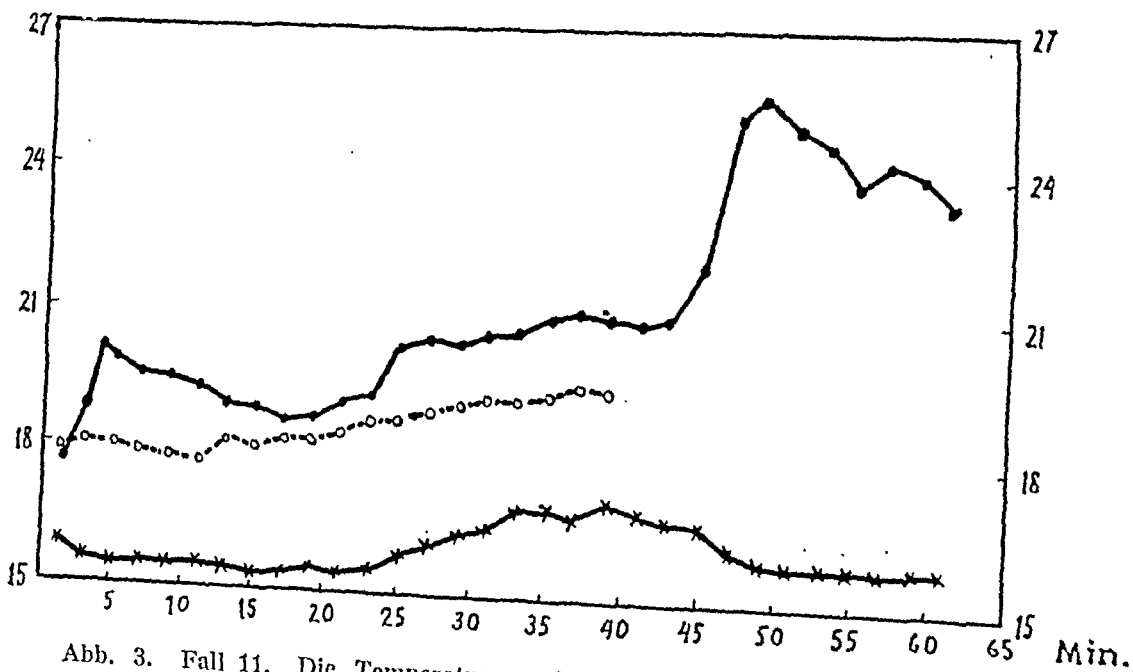


Abb. 3. Fall 11. Die Temperatur an der Spitze des rechten Daumens.  
 x-x-x-x-x = Kontrollversuch  
 o-o-o-o-o = Injektionsversuch. 15 Minuten vor Beginn der Messungen intramuskuläre Injektion von 0.02 g Priscol.  
 --- = Tablettenversuch. 26 Minuten vor Beginn der Messungen 0.05 g Priscol per os.  
 Zimmertemperatur bei allen Versuchen 14—15°.

Wasser genommen hat, sind sämtliche Finger stark ödematös geschwollen, was bei fortgesetzter Erwärmung allmählich etwas zurückgeht.

Bei einer Untersuchung bekam sie 2 Tabletten Priscol zu 0.025 g per os und tauchte ihre Hände 16 Minuten später in 15° warmes Wasser. Als sie die Hände nach 10 Minuten wieder herausnahm, hatten sie eine hellrote Farbe und die Fingerspitzen hatten eine Temperatur, die 1.5—2° über der des Kontrollversuchs lag. Während des weiteren Aufenthaltes in dem 14—15° warmen Zimmer stieg die Temperatur an den Fingerspitzen allmählich an, so dass nach 30 Minuten eine Temperatursteigerung von 3—4° stattgefunden hatte. An einzelnen Fingern trat eine leichte Schwellung auf. Ungefähr 45 Minuten nach Herausnahme der Finger aus dem Wasser erfolgte eine ziemlich rasche Temperatursteigerung mit weiteren 5—6° an sämtlichen Fingern (Siehe Abb. 3).

Als sie eine intramuskuläre Injektion mit 0.02 g Priscol, unmittelbar nachdem die Hände auf die übliche Weise abgekühlt worden waren, erhalten hatte, hielt sich die Fingerspitzentemperatur während der folgenden 15 Minuten im grossen und ganzen unverändert, begann jedoch dann einen langsamen Anstieg, der während der folgenden 10 Minuten 2—3° betrug. Die Finger begannen gerade in dem Moment, in dem die Injektion vorgenommen wurde, etwas anzuschwellen, aber die Schwellung trat nicht in dem Umfang auf, wie beim Kontrollversuch.

Bei einem anderen Versuch erhielt sie eine intramuskuläre Injektion mit 0.02 g Priscol, 5 Minuten ehe die Hände in das 15gradige Wasser getaucht wurden. Beim Herausnehmen aus dem Wasser 10 Minuten später, waren Hände und Finger hellrot, und die Fingerspitzen im Durchschnitt 1.5° wärmer als beim Kontrollversuch. Nachdem sich die Temperatur im grossen und ganzen während 15 Minuten konstant gehalten hatte, begann ein langsamer Anstieg, der während der folgenden 20 Minuten 2—3° betrug (Siehe Abb. 3). Nur unbedeutendes Anschwellen der Finger erfolgte.

Anfang April 1942 begann sie 3 mal täglich 1 Tablette Priscol zu 0.025 g zu nehmen, woraufhin es ihr rasch besser ging. Die Hände wurden wärmer und schwellen nur ausnahmsweise an, auch wenn sie sie in kaltem Wasser hatte. Keinerlei Unbehagen. Nach einigen Wochen konnte sie ihre Arbeit wieder aufnehmen. Die Beschwerden traten zwar wieder auf, wenn sie aufhörte die Tabletten zu nehmen, aber sie konnte die Dosis herabsetzen.

### *Fall 12) ♀. I. I., 22jährige Krankenschwesterelevin.*

Seit ungefähr 10 Jahren werden ihre Finger in der Kälte weiss, und sie klagte dabei auch über Steifwerden der Finger. Die Hände werden leicht zyanotisch.

Bei Abkühlung der Hände in 15° warmem Wasser werden die Finger weiss.

Experimentelle Untersuchungen über den Priscoleffekt wurden bei diesem Fall nicht vorgenommen.

Ab Mitte April 1942 wurde sie 3 mal täglich mit 1 Tablette Priscol zu 0.025 g behandelt. Es ging ihr daraufhin bedeutend besser, aber sie wurde

nicht frei von Beschwerden, indem eine Neigung zu Zyanose an den Händen bestehen blieb. Mitte Mai wurde die Behandlung abgebrochen, woraufhin die früheren Beschwerden fast unmittelbar wiederkamen. Sie rieb dann morgens und abends Finger und Hände mit 10 %iger Priscolsalbe ein, woraufhin es ihr besser ging, aber nicht so gut wie bei der Tablettenbehandlung. Als sie wieder zu dieser überging, wurden die Beschwerden wieder geringer.

Der folgende Fall verdient eine etwas ausführlichere Erwähnung, da es sich um Untersuchungen bei einem Fall handelt, bei dem beidseitig das unterste Halsganglion und die beiden obersten Brustganglien nebst dem zwischenliegenden Teil des Grenzstranges bei früheren Operationen exstirpiert worden waren.

**Fall 13)** ♀. S. J., 40jährige Postbeamtin.

Hat seit vielen Jahren an kalten und blauen Händen gelitten. Hände und Finger werden bei Abkühlung weiss und wenn sie wieder in wärmere Temperatur kommen, werden sie stark zyanotisch; fast schwarzblau. Sie arbeitete früher in einem während des Winters ziemlich kalten Lokal und musste den Arbeitsplatz wechseln, da sie so steife Hände bekam, dass sie ihrer Arbeit nicht mehr nachkommen konnte. Während des Jahres 1940 wurde sie mit praktisch genommen allen Mitteln behandelt, die in den Handbüchern gegen die Raynaudsche Krankheit empfohlen werden, ohne dass irgend ein Erfolg zu verzeichnen war. Eine Untersuchung im Februar 1941 nebst Untersuchung des Verhaltens der Fingertemperatur bei Erhöhung der Körpertemperatur zeigte das Vorhandensein einer spastischen Gefässaffektion, ohne Zeichen für Gefässverschluss. Da es ihr auch in normaler Zimmertemperatur Schwierigkeiten bereitete, ihrer Arbeit nachzukommen, erschien eine Operation indiziert. Es wurde daher am 24. 3. 1941 von Dr. A. Westerborn eine Exstirpation des untersten sympathischen Halsganglions und der beiden oberen Brustganglien sowie des dazwischen liegenden Teiles des sympathischen Grenzstranges der rechten Seite vorgenommen. Eine mikroskopische Untersuchung bestätigte, dass Ganglien und Grenzstrang entfernt worden waren. Unmittelbar nach der Operation wurde ihre rechte Hand warm und behielt auch bei Kälte normale Farbe. Am 8. 5. 1941 wurde vom gleichen Operateur eine entsprechende Operation auf der linken Seite vorgenommen, und auch hier wurde mikroskopisch bestätigt, dass Ganglien und Grenzstrang exstirpiert worden sind. Nach der Operation wurde auch diese Hand warm. Während des Sommers und Anfang Herbst 1941 war die Patientin ohne Beschwerden. Als es kälter wurde, kamen die Beschwerden wieder, jedoch weniger ausgesprochen als vor der Operation. Sie bekam leicht kalte und blaue Hände. Die drei radialen Finger der linken Hand waren jedoch in der Regel varm, und auch der rechte Daumen hatte die Neigung wärmer zu sein als die anderen Finger.

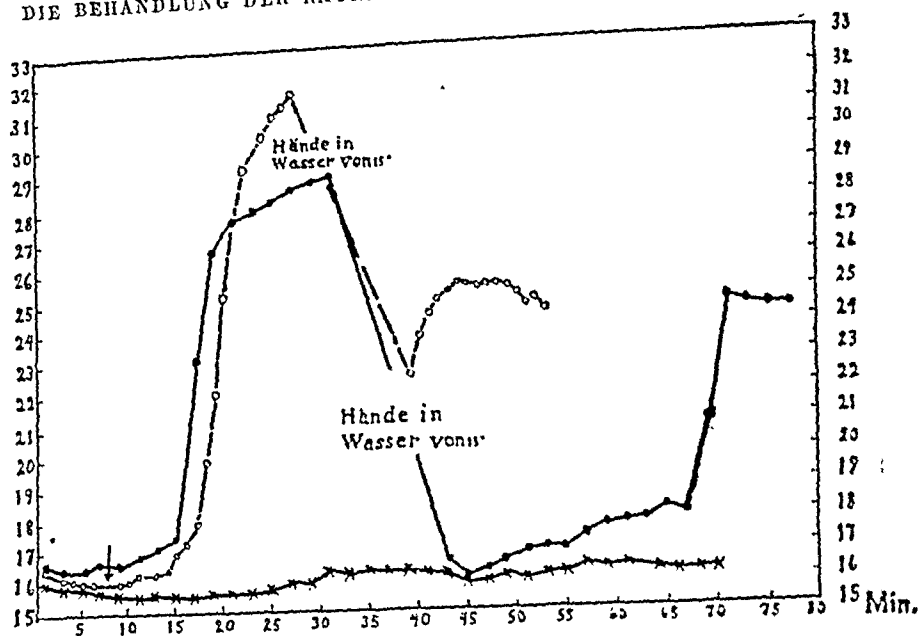


Abb. 4. Fall 13. Die Temperatur an der Spitze des rechten Mittelfingers.

x-x-x-x-x = Kontrollversuch

o-o-o-o-o = Injektionsversuch. Bei ↓ intramuskuläre Injektion von 0.02 g Priscol.

·-·-·-· = Tablettenversuch. 23 Minuten vor Beginn der Messungen 0.05 g Priscol per os.  
 Zimmertemperatur bei allen Versuchen 14–15°.

24°. Die Finger, die sonst kalt zu sein pflegten, waren 0.5–1° wärmer als sie sonst unter den gleichen Umständen ohne vorhergegangene Priscol-medikation waren. Sie begannen dann sich erst langsam und dann immer schneller zu erwärmen. Eine halbe Stunde nach Herausnahme der Hände aus dem Wasser hatten die Fingerspitzen eine Temperatur von 26.5–29°. Als die Hände nun aufs neue in 15° warmes Wasser getaucht wurden, wurden die Fingerspitzen fast genau so kalt wie beim Kontrollversuch, hatten aber eine rote Farbe und begannen fast unmittelbar eine höhere Temperatur anzunehmen; dieser Anstieg erfolgte erst langsam und dann sehr schnell. Noch 1 ½ Stunden, nachdem die Patientin Priscol bekommen hatte, ging also eine bedeutende Vasodilatation vor sich.

Abb. 4 veranschaulicht den Temperaturwechsel unter Einfluss von Priscol am rechten Mittelfinger der Patientin.

Als sie 3 mal täglich 1 Tablette Priscol zu 0.025 g nahm, litt sie stark unter Hitzegefühlen im Kopf und Klopfen im Kopf im Pulstakt sowie einem gewissen Schwindelgefühl. Dagegen war sie ihre Beschwerden an den Händen los geworden. Bei Herabsetzung der Priscoldosis verringerten sich die Kopfbeschwerden, aber dann waren die Hände nicht mehr beschwerdefrei, und es war nicht möglich eine Dosierung zu finden, bei der sie ohne Beschwerden an den Händen war, ohne dass gleichzeitig Kopfbeschwerden auftraten.

## Diskussion.

A) *Die Diagnose.* In zahlreichen Arbeiten über die Raynaudsche Krankheit steht man einigermaßen fragend vor dem Problem, was die Verfasser unter dieser Bezeichnung verstehen. In der vorliegenden Arbeit schliesse ich mich der von Lewis (11) gegebenen Definition an, dass man unter Raynaudscher Krankheit Fälle mit intermittierenden Spasmen in den Fingerarterien versteht. Dabei schliesse ich mich der Ansicht von Ekblom und Fogstrand (7) an, dass auch die Arterien der Zehen gleichzeitig affiziert sein können.

Die Diagnosestellung ging zunächst von den eigenen Angaben der Patienten aus, dass sie bei Kälte, und ein Teil der Fälle auch sonst weisse Finger bekamen. In der Mehrzahl der Fälle glückte es auch, durch Abkühlung der Finger in 15° warmem Wasser die typischen Veränderungen hervorzurufen. Bei anschliessender langsamer Erwärmung wurden Hände und Finger erst zyanotisch, dann blau mit roten Flecken und schliesslich rot. Fälle mit einfacher Akrozyanose sind also nicht im Material enthalten.

Bei den Fällen, bei denen Zweifel darüber herrschte, inwieweit ein Gefässverschluss als Ursache für die Beschwerden des Patienten vorgelegen haben kann, wie auch bei einigen anderen Fällen, wurde eine Messung der Fingerspitzentemperatur vorgenommen, während die Körpertemperatur des Patienten durch Verbringung der Füsse und Unterschenkel in 43—45° warmes Wasser erhöht wurde. Sobald die Dilatation in den Fingergefässen richtig eingesetzt hatte, verlief sie in allen Fällen sehr rasch und ergab eine Fingertemperatur von 33—35°, womit gezeigt ist, dass keine obturierende Gefässkrankheit vorlag. Nur bei einem Patienten (Fall 4) ergab der eine Daumen eine Temperatursteigerungskurve, deren Charakter den Verdacht einer leichten Obturation aufkommen liess. Fälle mit Bärger'scher Krankheit sind also nicht im Material enthalten. — Bei den Patienten, bei denen diese Erwärmungsversuche gemacht wurden, war auch die Zeit von Beginn der Erwärmung bis zum Einsetzen der Dilatation bedeutend länger als in den normalen Fällen, die ich auf entsprechende Weise untersucht habe [siehe Gask und Ross (10)]. Die Untersuchungsmethodik in der hier angewandten Form ist jedoch nicht genügend ausgearbeitet, um ohne weiteres eine Grenzziehung zwischen normalen Fällen und Fällen mit Raynaudscher Krankheit zu gestatten.



Bei der Mehrzahl der Fälle traten jedoch bei Aussetzen der Medikation die Beschwerden fast unmittelbar wieder auf; bei einigen Fällen gleich stark wie vor Beginn der Behandlung, bei anderen in gemilderter Form.

C) *Komplikationen.* Bei einem Fall (Nr. 1) musste die Behandlung abgebrochen werden, weil eine ausgesprochene Dermatitis an Fingern und Händen auftrat. Die Effloreszenzen erinnerten stark an die, welche man bei einer zu lange durchgeführten Histamin-jontophorese sehen kann, und haben möglicherweise eine gleichartige Genese, da Priscol ja eine Histaminkomponente enthält. — Das Auftreten dieser Komplikation habe ich in der früheren Literatur nicht erwähnt gefunden.

Bei einigen Fällen haben die Patienten über leichtes Schwindelgefühl während der Behandlung geklagt, und einzelne Fälle litten auch unter Frösteln nach Einnahme der Tabletten. Bei einem Fall trat in direktem Anschluss an eine intramuskuläre Injektion von 0.02 g Priscol starker Schwindel mit Kollapstendenz auf. Auch Frösteln ist bei einigen Fällen im Anschluss an die Injektion aufgetreten; bei einem Fall (Nr. 9) mit starkem Schüttelfrost.

Magenbeschwerden traten bei keinem Fall meines Materiales auf (dagegen musste ich bei einem Fall von Morbus Bürger die Behandlung abbrechen, da der Patient saueres Aufstossen bekam).

*D) Die Versuchsbedingungen bei den Hauttemperaturmessungen.*

Bei den in der Literatur genannten Untersuchungen über den Effekt vasodilatierender Mittel, wird in der Regel garnicht die Frage berührt, auf welche Weise die Untersuchung angeordnet wurde, um eine Garantie dafür zu haben, dass die eventuell auftretenden Veränderungen wirklich ein Effekt des zugeführten Präparates sind und nicht »spontan« auftraten. Im allgemeinen scheint man es als selbstverständlich zu betrachten, dass, wenn man nur eine Person konstanten äusseren Bedingungen aussetzt, nach einer Weile auch konstante Hauttemperatur eintritt. Die einzigen wirklichen Untersuchungen über das Verhalten der Hauttemperatur bei konstanten äusseren Bedingungen, die ich habe finden können, stammen von Roth, Horton und Sheard (12). Diese Untersuchungen zeigen, dass auch bei ausserordentlich genau standardisierten Verhältnissen Veränderungen der Fingerspitzentemperatur von 3—4° sehr wohl bei Normalfällen vorkommen können. Da deren Material klein war, ist die Variationsbreite bei einem grösseren Ma-

terial wahrscheinlich bedeutend grösser. Bei einigen vorbereitenden Untersuchungen fand ich auch unter ziemlich konstanten äusseren Bedingungen bedeutende Veränderungen der Fingerspitztemperatur innerhalb kurzer Zeitspannen, wenn die Versuchsperson sich in gewöhnlicher Zimmertemperatur aufhielt.

Ich versuchte dann zunächst, meine Untersuchungen so durchzuführen, dass der Patient in ein so kaltes Zimmer verbracht wurde, dass die Fingerspitztemperatur langsam aber deutlich sank. Wenn dann nach Zuführung von Priscol die Fingerspitztemperatur stieg, sollte dies als ein sichergestellter Effekt des Präparates betrachtet werden können.

Weitere Beobachtungen der Fingertemperatur der Patienten während ihres Aufenthaltes in kaltem Zimmer zeigte jedoch, dass der genannte Schlussatz nicht als sicher betrachtet werden konnte. So ergaben Messungen bei Fall 7 bei einer Untersuchung nach einer langsam von statten gehenden Temperatursenkung eine »spontane« Temperatursteigerung, die am rechten Mittelfinger in 8 Minuten  $5.4^{\circ}$  betrug; von  $19.1^{\circ}$ — $24.5^{\circ}$ . Während der folgenden 6 Minuten trat eine Temperatursenkung mit  $3^{\circ}$  ein, aber gleichzeitig während diese Senkung vor sich ging, stieg die Temperatur am rechten kleinen Finger von  $16.3^{\circ}$  auf  $23.5^{\circ}$ . Es ist selbstverständlich bei so starkem spontanen Wechsel der Fingertemperatur unmöglich, sich ein sicheres Urteil über den Effekt der Zuführung des einen oder anderen Stoffes zu bilden. Ich wage daher auch keine Schlüsse aus den Versuchen zu ziehen, die mit dieser Methodik bei Fall 1 und 5 ausgeführt worden sind.

Carmichael und Mitarbeiter [siehe z. B. Uprus, Gaylor und Carmichael (13)] haben auch in einer Reihe von Arbeiten gezeigt, dass eine Untersuchung der Vasokonstriktion wertlos ist, wenn sich der Patient dabei nicht in hochgradiger Vasodilatation befindet, und zwar wegen der »spontanen« Schwankungen im Gefäßtonus bei einem Zustand zwischen starker Dilatation und starker Konstriktion. Bei Untersuchungen der Vasodilatation sollte man daher, mutatis mutandis, von einem Zustand ausgehen, bei dem der Patient sich in Vasokonstriktion befindet, wie es auch von Stürup betont worden ist (14).

Zahlreiche Beobachtungen haben gezeigt, dass es möglich ist, einen Patienten mit Raynaudscher Krankheit bei relativ konstanter Fingerspitztemperatur zu halten, wenn man seine Hände in  $15^{\circ}$

warmes Wasser bringt und ihn sich dann in einem Zimmer mit einer Temperatur von oder etwas weniger als  $15^{\circ}$  aufhalten lässt [siehe Lewis (11), Gask und Ross (10)]. Meine Untersuchungen zeigten jedoch bald, dass die genannten Bedingungen nicht stets eine konstant niedrige Fingertemperatur garantieren. Bei einem Teil meiner Fälle trat nämlich ziemlich schnell eine bedeutende Steigerung der Fingerspitzentemperatur ein; manchmal langsam, manchmal schnell. Es zeigte sich, dass die Kleidung des Patienten von entscheidender Bedeutung für die eventuelle Temperatursteigerung war; war er warm gekleidet, trat leicht eine Temperatursteigerung ein, die ausbleiben konnte, wenn er weniger Kleider an hatte. Man muss daher bei jedem Fall ausprobieren, bei welcher Kleidung sich die Fingerspitzentemperatur des Patienten unter den genannten Versuchsbedingungen während längerer Zeit konstant hielt. Kleinere Schwankungen waren allerdings unvermeidlich. Bei den nachfolgenden Untersuchungen mit Priscolgaben musste der Patient ganz genau so angezogen sein, und es wurde genau darauf geachtet, dass die Zimmertemperatur bei diesen späteren Untersuchungen nicht höher war als beim Kontrollversuch.

Mit dieser Methode erreicht man, dass eine Temperatursteigerung, die nach Verabreichung einer Medizin auftritt, als eine Folge dieser Verabreichung betrachtet werden kann. Ausserdem untersucht man den Effekt des Medikaments auf den Patienten dabei unter Verhältnissen, unter denen der Patient wirklich Beschwerden auf Grund seiner Krankheit hat. Ein Nachteil dieser Methode ist jedoch, dass man eine so starke Vasokonstriktion hervorgerufen haben kann, dass die zugeführte Dosis sie nicht zu überwinden vermag, während man bei einem etwas geringeren Grade von Vasokonstriktion, der doch ausreichend gewesen wäre, um eine konstante, niedrige Fingertemperatur und auch subjektive Symptome zu erzeugen, einen Erfolg hätte verzeichnen können. Das Ausbleiben eines messbaren Effektes braucht daher nicht zu bedeuten, dass das Präparat in der verabreichten Dosis unwirksam ist.

E) *Die Resultate der experimentellen Untersuchungen mit Verabreichung von Priscol.* Wenn die Patienten, ohne der Priscol-Einwirkung ausgesetzt gewesen zu sein, ihre Hände unter den gewöhnlich angewandten Versuchsbedingungen in  $15^{\circ}$  warmes Wasser gehalten hatten, waren Hände und Finger entweder weiss oder zyanotisch. Bei 14 Untersuchungen an 9 verschiedenen Patienten

wurde dem Patienten Priscol entweder per os oder durch intramuskuläre Injektion, 15—30 Minuten ehe er die Hände aus dem Wasser nahm, zugeführt. Bei 6 dieser Fälle hatten Hände und Finger beim Herausnehmen aus dem Wasser eine hellrote Farbe, bei 5 Fällen waren sie wie beim Kontrollversuch, und in den anderen 3 Fällen waren die Fingerspitzen zyanotisch, während die übrigen Teile von Fingern und Händen hellrot waren. Schon aus diesen unmittelbaren Beobachtungen geht klar hervor, dass Priscol bei vielen Fällen einen Einfluss auf die Zirkulation in den Fingern bei Abkühlung ausübt.

Bei 13 der genannten Untersuchungen konnte man die Fingerspitzentemperatur unmittelbar nachdem die Hände aus dem Wasser genommen und abgetrocknet worden waren, mit den entsprechenden Temperaturen beim Kontrollversuch vergleichen. Bei nur zweien dieser Versuche lag die Temperatur beim Priscolversuch niedriger als beim Kontrollversuch, bei den anderen höher. Im Durchschnitt war die Temperatur beim Priscolversuch  $0.80 \pm 0.277^\circ$  höher. Da die Differenz beinahe genau 3 mal ihr mittlerer Fehler ist, muss sie praktisch gesehen als sichergestellt betrachtet werden.

(Auf Grund der Berechnungsart für den mittleren Fehler ist dieser etwas zu gross geworden. Bei jedem Patienten wurden die Messungen in der Regel an allen Fingern vorgenommen, in einigen Fällen nur an 4 oder 6 Fingern. Für jeden einzelnen Finger wurde die Differenz zwischen Priscolversuch und Kontrollversuch berechnet, und dann wurde der Mittelwert zwischen diesen Differenzen für jeden einzelnen Patienten ausgerechnet. Auf dieser letztgenannten mittleren Differenz basierte also die Berechnung des Mittelwertes der Temperatursteigerungen und dessen mittleren Fehlers bei der ganzen Versuchsreihe. Die Berechnung wurde also so vorgenommen, als ob bei jedem Patienten nur eine Messung vorgenommen worden wäre. Der so erhaltene mittlere Fehler wäre richtig unter der Voraussetzung, dass zwischen den verschiedenen Fingern ein und desselben Patienten keine Variationen vorlägen. Hätte man statt dessen den Mittelwert für die Differenz bei allen 90 Fingern, bei denen Messungen gemacht wurden, berechnet, sowie den mittleren Fehler für diesen Mittelwert, hätte man einen mittleren Fehler von nur 0.11 erhalten. Die Voraussetzung dafür dass diese letztere Berechnungsart erlaubt wäre, wäre, dass die verschiedenen Finger ein und desselben Patienten unabhängig von einander variierten. Man kann nicht davon ausgehen, dass dies der Fall ist, wenn auch bedeutende Variationen vorkommen. Der mittlere Fehler des Mittelwertes liegt daher zwischen 0.11 und 0.277).

Bei den 7 Versuchen an gleich vielen Patienten, bei denen der Patienten vor Beginn der Abkühlung zwei Tabletten Priscol zu

0.025 g per os erhalten hatte, war die Fingerspitzentemperatur eine halbe Stunde nach Herausnehmen der Hände aus dem Wasser nur bei einem Fall unbedeutend niedriger als im gleichen Zeitpunkt des Kontrollversuches; bei allen anderen Fällen höher. Die höchste Steigerung betrug im Mittelwert für einen Patienten  $6.3^{\circ}$ , und an einem einzelnen Finger  $13^{\circ}$ . Der Mittelwert der Steigerung betrug  $3.04 \pm 0.84^{\circ}$  (der mittlere Fehler berechnet, als ob der Mittelwert für die Beobachtungen einer einzelnen Beobachtung gegolten hätte, so dass auch hier der mittlere Fehler zu gross ist). Da der Mittelwert mehr als dreimal sein mittlerer Fehler ist, muss die Differenz als sichergestellt betrachtet werden. Es tritt also unter dem Einfluss von Priscol-Tabletten eine deutliche Temperatursteigerung an den Fingerspitzen ein. — In gewissen Fällen setzte sich diese Steigerung nach einer halben Stunde weiter fort, bei anderen trat eine langsame Senkung der Temperatur ein.

Bei den 9 Fällen, bei denen 0.02 g Priscol intramuskulär injiziert wurde, trat bei allen Fällen eine Temperatursteigerung ein, die bei der Mehrzahl schon einige Minuten nach der Injektion begann. Eine halbe Stunde nach der Injektion war die Steigerung im Mittelwert für einen Patienten mindestens  $1.6^{\circ}$  und höchstens  $12.3^{\circ}$  mit einem höchsten Wert von  $13.4^{\circ}$  für einen einzelnen Finger. Der Mittelwert für die Steigerung bei allen Fällen betrug  $5.4^{\circ} \pm 1.06^{\circ}$ , also eine statistisch sichergestellte Differenz. Intramuskuläre Injektion von Priscol in Dosen von 0.02 g erzeugt also eine bedeutende Steigerung der Temperatur an den Fingerspitzen.

Bei den nun genannten Berechnungen sind die Resultate von Fall 13 nicht berücksichtigt worden, da dieser Fall insofern von den anderen abweicht, als hier eine Entfernung der Sympathikusinnervation nach den Armen vorgenommen worden ist. Aus früher genannten Gründen muss man annehmen, dass diese Entfernung vollkommen war. Auch bei diesem Fall hatte Priscol sowohl per os als auch bei intramuskulärer Injektion einen starken dilatierenden Effekt auf die Gefässe des Kopfes und der oberen Extremitäten. Von besonderem Interesse ist folgendes: An den zwei ulnaren Fingern der linken Hand und der vier ulnaren Fingern der rechten Hand, deren Gefässe vor der Operation auf normale Weise durch Erhöhung der Körpertemperatur der Patientin dilatiert worden waren, war es nicht möglich, nach der Operation auf entsprechende

Weise eine nennenswerte Temperatursteigerung zu erzielen. Aber an den gleichen Fingern bekommt die Patientin bei Aufenthalt in einem 15° warmen Zimmer und nach Abkühlung in 15gradigem Wasser eine hochgradige Temperatursteigerung nach Zuführung von Priscol. — Ein so starker Effekt wie bei diesem Fall war kaum bei irgend einem anderen Patienten zu verzeichnen.

F) *Die Wirkungsart von Priscol.* Auf welche Art Priscol die erhöhte Blutdurchströmung erzeugt, ist noch ungeklärt. Hartmann und Isler (1) vermuten eine Einwirkung auf die Arterioli. Meier und Müller (8) reden vom »Angriffspunkt in medullär-spinalen und peripher gelegenen Mechanismen«, aber es geht aus ihrer Arbeit nicht hervor, worauf sie diese Auffassung stützen.

Theoretisch kann man sich verschiedene Möglichkeiten denken:

1. eine Einwirkung direkt auf die Gefäße, ohne eine Vermittlung irgendwelcher Nervenbahnen.

2. ein Aufheben oder eine Verminderung der vasokonstriktorische Impulse durch den Sympathikus.

3. eine Reizung via vasodilatatorische Elemente im Sympathikus, deren Existenz von vielen Forschern angenommen wird [Lewis und Pickering (15), Grant und Holling (16), Fatherree und Allen (17)],

4. eine Reizung der Vasodilatoren in den sensibeln Nerven.

Priscol hat nach den Ergebnissen von Fall 13 der vorliegenden Untersuchung einen ausgesprochen vasodilatierenden Effekt, auch auf Gefäße, die jeder Innervation von Seiten des Sympathikus beraubt sind. Man muss daher annehmen, dass entweder eine direkte Einwirkung auf die Gefäße oder eine Einwirkung auf dem Wege über die sensiblen Nerven vorliegt.

Die besonders schnelle Temperatursteigerung, die bei einem Teil der Fälle nach Verabreichung von Priscol eintrat, kann nicht nur durch eine Dilatation der Arterioli erklärt werden, sondern muss auf einer Eröffnung der arteriovenösen Anastomosen in den distalen Teilen der Finger beruhen [Grant und Blend (18), siehe auch die Zusammenfassung bei Brack (3)]. Hierin liegt auch die Erklärung dafür, dass die Temperatursteigerung bei einem Teil der Fälle rascher an den Fingerspitzen als an den Fingerbasen erfolgte.

## Zusammenfassung.

Priscol wurde bei 12 mittelschweren Fällen mit Raynaudscher Krankheit angewandt. Alle diese Patienten fühlten sich besser, als sie das Präparat nahmen; 6 waren ganz frei von Beschwerden, weitere 3 waren fast frei von Beschwerden, während die restlichen 3 nur unbedeutende Linderung verspürten. Nebenwirkungen in Form von Schwindel oder Frösteln waren unbedeutend.

Hauttemperaturmessungen an den Fingerspitzen zeigten, dass Priscol sowohl bei peroraler als auch bei intramuskulärer Verabreichung einen vasodilatierenden Effekten ausübte. Die geeigneten Versuchsanordnungen bei derartigen Untersuchungen werden eingehend diskutiert.

Auch bei einem Fall, bei dem die Sympathikusinnervation der Arme vollkommen entfernt worden war, hatte Priscol einen starken Effekt auf die Durchblutung der Finger. Von dem letztgenannten Fall ausgehend, wird der Wirkungsmechanismus diskutiert.

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(From the Medical Department of the Roskilde County Hospital, Denmark. Physician in Chief: J. E. Holst, Dr. med.)

## Chemotherapeutical Treatment of severe Colitis and Proctitis.

By

J. E. HOLST.

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The treatment of severe, ulcerative, suppurative colitis is often extremely difficult. The immediate results are frequently unsatisfactory, and there is also a great tendency to relapse. Any new treatment which is able to improve our therapeutic results in this field must therefore always be of interest.

In »*Nordisk Medicinsk Tidskrift*», 1940, N. Svartz and N. Kallner (1) have reported on some very interesting results of treatment with Sulphapyridine in ulcerative colitis. Svartz and Kallner sum up their experiences as follows:

1) In a number of cases there was an immediate cure, and this might occur even in cases of long duration. In particularly favourable cases it was seen that the effect on the diarrhoea set in after a few days' administration, and that the proctoscope also revealed an improvement of the rectal mucosa within a few days.

2) In a number of cases there was some improvement, but no complete cure.

3) In other cases the treatment had no effect whatever.

4) Finally, in a few cases a certain aggravation with an increased tendency to haemorrhage was observed.

In 1941 N. Svartz (2) published a new report on an attempted treatment with a combined preparation of salicylic acid and Sulpha-

pyridine called Salazopyrin. Her experience was that the effect of Salazopyrin on ulcerative colitis was still more evident than that obtained from treatment with Sulphapyridine. Some cases which had improved but had not been cured by Sulphapyridine recovered on Salazopyrin. It also appeared, however, that some cases were totally unaffected by Salazopyrin.

As a suitable initial dose Svartz gives 1 gramme 4—6 times a day, and, if necessary, the treatment may be continued for weeks and months. Complicating effects are not very pronounced, the most frequent being exanthema of a morbilliform or scarlatini-form type, or a rise in temperature (a slight rise does not necessitate discontinuation of treatment).

Later Öhnell (3) published his experiences from treating 22 patients suffering from suppurative colitis with Sulphapyridine, Uliron, Sulphathiazol, Salazopyrin, Sulphonamid, or Albucid, 20 of which presented favourable results.

The reports from Sweden induced the staff of the Medical Department of the Roskilde County Hospital to try the above treatment on a small number of cases. As it was not possible to obtain Salazopyrin at once, we had in some instances to use other preparations, as will be seen from the case records in question. The latter have been abbreviated as much as possible, only circumstances relevant to the subject having been included.

**Case 1.** E. E. A. 30-year old female (No. 529/1941). Admitted March 7th, 1941, Discharged April 26th, 1941.

Since 1941 periodical depression, otherwise no previous major illness. 3 weeks before entering the hospital the patient, who formerly had a tendency to constipation, began to suffer from diarrhoea, and since then her bowels have opened as much as 10 times a day. The stools have contained mucus and blood. No dyspeptic symptoms otherwise.

Physical examination revealed nothing abnormal. General condition good. Height 161 centimetres. Weight 70.1 kilos. Urine contained nothing pathological. Hmgb percentage: 110. Sedimentation rate of red blood corpuscles 6 millimetres/1 hour. Widal test: ÷. Frey test: ÷. Ascorbic acid in serum: 0.36 mg per 100 cm<sup>3</sup>.

Temperature slightly higher than normal just over 38° C in the evening, 37.5—37.7° C in the morning.

|        | 8/3 | 10 | 11 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|--------|-----|----|----|----|----|----|----|----|----|----|----|
| Blood  | ++  | ++ | ++ | ++ | +  | ++ | ++ | ++ | ++ | ++ | ++ |
| Faeces |     |    |    |    |    |    |    |    |    |    |    |
| Mucus  |     |    |    | ÷  | ÷  | ÷  | ÷  | ÷  | +  | +  | ÷  |

Rectum as examined in proctoscope: Mucous membrane nobbly, bright red, haemorrhagic.

Immediately after admission treatment with raw, grated apple was given.

This had no effect on the diarrhoea, stools remaining loose with 4—5 openings daily and highly positive blood reaction. Apples were given until March 15th, and then the patient was put on a light diet and received Laudanum, 15 drops 4 times a day. M & B 693 was also given in the following doses:

March 15th—March 16th 1 gramme 6 times daily ( $\frac{1}{2}$  teaspoonful,  $\text{NaCHO}_3$  with each dose)

March 17th—March 22th 0.5 gramme 6 times daily (28 grammes in all)

As there was no effect of M & B the administration was discontinued. again two days' diet of raw apple, and after that a light diet was given together with Bis. Sal., 2 g 3 times daily.

From March 29th enemas of *Calcii carbonatis praecip.* 50 g  
*Mucil. gi. arabic.* 100 "  
*Aqua* ad  $\frac{1}{2}$  litre

were given — 250 cm<sup>3</sup> every night.

At that time a slow improvement set in. From March 27th the temperature remained normal, the number of evacuations gradually decreased, diarrhoea was last observed on April 5th, and during the last week there was only 1 semisolid evacuation a day. On the patient's discharge the stools still contained blood, but the reaction was less pronounced than at the time of her admission.

The mucosa as seen in the proctoscope (April 17th) showed considerable improvement, but it was still somewhat swollen in places with a tendency to haemorrhage. Bis. Sal., 2 g once a day, was still administered.

**Case 2.** E. T. H. N. 48-year old female. Admitted May 12th, 1941.

No previous major illness.

In April 1939 the patient underwent treatment for mucous, haemorrhagic diarrhoea at the St. Maria Hospital, Roskilde. After that she felt well until January 1941, when diarrhoea occasionally occurred. During the last 4 weeks before admission her condition grew worse, so that she passed loose, mucous, malodorous stools 2—3 times a day. Otherwise no dyspeptic symptoms. A slight loss of weight.

Physical examination revealed nothing abnormal. General condition good. Height 164 cm. Weight 51.1 kilos. Hmgb percentage: 93. Sedimentation rate of red blood corpuscles: 10 mm/1 hour. Ascorbic acid in serum: 0.48 mgs per 100 cm<sup>3</sup>.

Ewald's test meal: 1 hour: 0.

40 min.: 95 + 8 cm well digested. Kongo figure: 35, phenolphthalein 65.

|                        |      |    |    |    |    |    |     |
|------------------------|------|----|----|----|----|----|-----|
|                        | 13/5 | 14 | 15 | 16 | 17 | 18 | 19  |
| Blood (benzidine test) | ++   | ÷  | ÷  | +  | ÷  | ÷  | +++ |

Faeces:

Catalase figure

40 86 10

Urine & faeces: No pathogenic bacteria.

Temperature: Normal.

Rectal mucosa (15 cm): Swollen everywhere, nobbly, bright red, haemorrhagic in parts.

X-ray examination of the colon (March 15th): The emulsion entered quite easily filling the rectum, colon and caecum without defects. The limits of the contrast somewhat blurred. After opening of the bowel very slight emptying.

(X-ray diagnosis: Nothing definitely abnormal).

During the first part of her stay the patient was given a light diet, *calcii carbon.*, *calcii phosph. praecip.* aa parts, vitamin C, and the following enema every night:

|                                  |       |                        |
|----------------------------------|-------|------------------------|
| <i>Calcii carbon. praecip.</i>   | ..... | 50 grs                 |
| <i>Mucil. gummi arabic.</i>      | ..... | 100 »                  |
| <i>Aquae</i>                     | ..... | ad 500 cm <sup>3</sup> |
| 250 cm <sup>3</sup> every night. |       |                        |

As the patient still passed stools 2—3 times per day, sometimes solid or loose, but most often semi-solid, chemotherapy was instituted as below:

|         |                      |   |        |   |       |       |
|---------|----------------------|---|--------|---|-------|-------|
| 3/6—4/4 | M & B 693            | 1 | gramme | 6 | times | daily |
| 5/6     | Staphylamid (Sulpha- | 1 | »      | 6 | »     | »     |
|         | methyliiazol)        |   |        |   |       |       |

up to 18 grammes.

At this stage treatment was discontinued on account of nausea and discomfort. At the same time the condition was aggravated with the number of loose evacuations increasing to 9 times a day on June 12th.

Since then it was not possible to get the patient into a satisfactory condition in spite of dieting, apple treatment, *pulvis calcis bismuthicus*, nicotinic acid, vitamin-B compound (liver and yeast preparation), laudanum etc. Her hmgb. percentage fell to 68, the weight to 40.7 kilos. At the beginning of November she passed stools containing mucus and blood 7—8 times a day. Treatment with Salazopyrin was then commenced:

|                    |   |        |   |       |                    |
|--------------------|---|--------|---|-------|--------------------|
| Nov. 5th—Nov. 21st | 1 | gramme | 4 | times | daily              |
| Nov. 22nd—Dec. 9th | 1 | »      | 3 | »     | » (120 grs in all) |

During this treatment an improvement was noticed, the faeces became slightly more solid, but when the administration of Salazopyrin ceased, the patient's condition was as before.

X-ray examination (Dec. 16th): Contrast entered easily and quickly through the relaxed bowel, which appeared as a smooth, flaccid tube with slightly uneven outlines. All haustra had disappeared, only in the colon descendens some vague, broad, unevenly distributed constrictions resembling haustra were seen. Rectal conditions as examined in proctoscope: unchanged.

During spring and early summer of 1942 there was a very slow improvement of her condition. Her hmgb. percentage rose to 95 %, her weight

to 61.5 kilos (10 kilos more than her weight on admission). Stools were no longer loose, and in June 1942 there were generally 5 semi-solid evacuations per day. The patient was still in the hospital, when this paper was published.

**Case 3.** II-year old boy. (No. 1340/1941). Hospitalised May 15th—July 10th and Oct. 27th—Nov. 13th 1941.

Since the age of 9 months the patient had had continuous intestinal trouble with diarrhoea, sometimes acute feverish phases of a few days' duration. Since 1934 there had nearly always been blood in the stools, both directly visible as small stripes and clots and also shown by benzidine test.

In the following years the benzidine test constantly showed blood in the stools. In periods they might be normal on a light diet and Bis. Sal., but were more often semi-solid and, periodically, loose. It was difficult to maintain a normal hmg. percentage (in 1939 49 only), but it rose regularly, when iron was given. In 1935, 1937, and 1939 repeated attacks of pains in the epigastrium occurred with the temperature rising to 39° C, vomiting, dark coloured urine, light coloured stools and occasional slight jaundice. From 1939 tonsillitis repeatedly occurred with fever and articular pains of a few days' duration, almost all joints being affected. There were no signs of hemeralopia or pellagra, but there was a tendency to gum-bleeding when the patient brushed his teeth. In 1935, 1936 and 1937 the patient was hospitalised. Below are some of the examinations made during these periods:

Ewald's test meal: 13 + 5 cm<sup>3</sup> Kongo figure: 43. Phenolphthalein: 60.

Faeces: Constant +++ blood, + mucus.

Rectal examinations: 1935: Nothing abnormal.

1938: 10 centimetres from the anus slightly haemorrhagic, superficial erosions.

X-ray examinations: 1935: Stomach, small intestine, colon: Nothing abnormal.

1936: Stomach, intestine: Nothing abnormal, Hepatic ducts following tetraiodide-phenolphthalein sodium: No shadow of gall-bladder.

1938: The haustra of the intestine somewhat less pronounced than normally, otherwise nothing abnormal.

The patient was re-admitted on May 13th 1941. For the last months he had suffered from diarrhoea 2—3-times a day, occasional pains in the epigastrium and vomiting. He was pale and thin, the temperature reaching a maximum of 38.5° C in the evening and 37.6° C in the morning. The abdomen was slightly distended and tender. On May 30th there was slight bleeding from the nose and a spasm of painful rigidity of the left hand, which was held in a typically tetany attitude.

Height: 141 cm. Weight 26.8 kilos. Hmgh percentage 82. Sedimentation rate of red blood corpuscles 27 mm/1 hour. Icteric index: 4 (Meulengracht).

|                        |      |      |      |    |    |     |    |
|------------------------|------|------|------|----|----|-----|----|
| Blood (benzidine test) | 13/5 | 14   | 15   | 17 | 18 | 19  | 20 |
| Faeces:                | +++  | +++  | ++   | ++ | ÷  | ++  | ++ |
| Catalase figures       | 100  | 100  | >100 | 66 |    | 100 | 86 |
| Serum calcium 15/5     | 31/5 |      | 11/6 |    |    |     |    |
|                        | 8.9  | 10.0 |      |    |    |     |    |

Ascorbic acid in serum: 0.16 1.68

X-ray examination (May 15th): The emulsion entered fairly easily filling the rectum, colon and coecum. The intestine was narrow, rigid and without haustra. The inner surface was nobbly. Only the rectum and lower part of colon sigmoideum could be distended. After passing of stools only moderate emptying was observed, and the mucous membrane was but slightly folded. The folds were lying in a coarsely meshed reticulum indicating atrophy of the mucosa. The stomach showed nothing abnormal.

At this stage chemotherapy was instituted in the following manner:

|                   |           |                  |               |
|-------------------|-----------|------------------|---------------|
| May 19th—May 21st | M & B 693 | 0.75 g           | 6 times daily |
| May 22nd—May 25th | M & B 693 | 0.50 g           | 6 " "         |
| May 26th—May 27th | M & B 693 | 0.50 g           | 3 " "         |
|                   |           | (28.25 g in all) |               |

In connection with the treatment his condition changed rapidly. Already on the second day the faeces became semi-solid, and on his leaving hospital there was one fairly solid evacuation per day (pulvis calcis bismuthicus — 1 teaspoonful twice daily having been given). The temperature remained subfebrile until May 15th and from that day normal. The weight increased from 26.8 to 31.9 kilos.

X-ray control (July 3rd): The colon was now considerably more resilient than at the previous examination. The colonic lumen was normal, but when filled it was quite smooth without haustra. After defaecation fairly good emptying was observed, and when the intestine was not dilated a certain number of haustra were seen. As the above attacks of tonsillitis, rises in temperature, and articular pains continued after his discharge the patient was re-admitted on Oct. 10th, 1941. The tonsils were found to be enlarged, grooved and showing cheesy matter, and tonsillectomy ad modum Sluder was done on Oct. 29th, 1941, after preceding intravenous treatment with Soluchinon (K-vitamine) to safeguard against haemorrhage.

As stools were still semi-solid in spite of administration of calcis bismuthicus (in doses of 1 teaspoonful 3 times daily) Salazopyrin was given as below:

|                         |        |                           |
|-------------------------|--------|---------------------------|
| Nov. 5th—Nov. 10th      | 1 g    | 3 times per day           |
| " 11th— " 20th          | 1 g    | 2 " " "                   |
| " 21st— " 27th          | 0.5 g  | 3 " " "                   |
| " 28th—Dec. 4th         | 0.5 g  | 2 " " "                   |
| Dec. 5th—Feb. 3rd, 1942 | 0.5 g  | 1 " " "                   |
| Feb. 4th—Mar. 6th       | 0.25 g | 1 " " " (95.75 g in all). |

Already the first day after treatment had been commenced, stools were normal, although pulvis calcis bismuthicus was dispensed with.

Out-patient control on June 13th, 1942: Since November stools had been solid and passed daily or at intervals of 1 or 2 days. Neither blood nor mucus had been observed. Hmgb. percentage: 87. Weight: 35 kilos. Height: 145 cm. Subjective condition: Excellent. The patient had been free of articular pains for several months.

X-ray examination: After enema the condition of the colon was on the whole the same as on July 3rd, 1941. When filled practically the whole colon was smooth in outline, and there was a complete absence of haustra with exception of a few small protuberances in the ascending part. After evacuation there was a clear tendency to haustra both in the transverse and the descending colon. This tendency seemed stronger than the previous year.

**Case 4.** E. J. N. 30-year old male (No. 271/1942). Hospitalised May 21st—July 11th, 1941, and Jan. 14th—Feb. 24th, 1942.

No previous major illness. For about 3 years the patient has suffered from tardy pains in the epigastrium with relief after meals, nausea but no vomiting. Stools had been normal. During the last 6 months the patient had lost 5 kilos in weight.

Physical examination revealed nothing abnormal. General condition good. Temperature normal.

Height: 162 cm. Weight: 51 kilos. Hmgb. percentage: 100. Sedimentation rate of red blood corpuscles: 5 mm/1 hour. Ascorbic acid in serum: 0.24 mgs per 100 cm<sup>3</sup>.

Ewald's test meal (1 hour): 110 + 15 cm<sup>3</sup> well digested without mucus. Kongo figure: 70. Phenolphthalein: 95.

Faeces: Constant ++ blood (benzidine test).

X-ray examination: Gastro-duodenitis, duodenal ulcer?

As the pains were supposed to originate from the gastro-duodenitis, the patient was put on a diet of egg and milk on May 27th. The pains, however, were almost more severe than before, and from May 30th the patient suffered from diarrhoea, during the following days passing watery stools containing plenty of fresh, red, partly coagulated blood 4—5 times a day.

On June 4th the rectum (10—12 cm) was bright red and swollen; higher up the mucosa was not visible, as the field was flooded with blood.

Together with the diet chemotherapy was now instituted, 6 grammes of Stafylamid (Sulphamethylthiazol) being given once a day. But already the next day this administration had to be discontinued on account of repeated vomiting. For some time loose, haemorrhagic stools were frequently passed. The temperature rose to a maximum of 39°C. between May 8th and May 20th. The hmgb. percentage fell to 67.

With continued dieting and administration of pulvis calcis bismuthicus a gradual improvement set in. The hmgb. percentage rose to 103. From June 14th no blood was visible in the faeces, and from June 21st the ben-

*zidine test was negative.* On his discharge the patient felt completely well, solid stools being passed once a day.

Control of rectal mucosa on July 3rd: Mucosa almost normal with a few superficial erosions and slight bleeding.

On the patient's re-admission in January 1942 the mucosa was normal for 25 cms.

**Case 5.** A. G. P. 26-year old female (No. 580/1942). Admitted Feb. 12th Discharged Apr. 23th, 1942.

No previous major illness.

10 days before admission the patient began to suffer from diarrhoea with up to 15—20 daily evacuations, stools were watery, but contained neither mucus, blood nor pus. The last few days the temperature rose to 38° C in the evening, and the patient vomited after all meals. No effect on the diarrhoea was obtained by red rest, grated raw apples and laudanum.

Physical examination: Nothing abnormal.

General condition: Good.

Height 175 cm. Weight: 55.5 kilos (69 kilos 2 months previously). Hmgb. percentage: 91: Sedimentation rate of red blood corpuscles: 2 mm/1 hour. Ascorbic acid in serum: 0.08 mgs per 100 cm<sup>3</sup>.

Faeces contained mucus, but after 5 days no blood. Catalase figure 2.

No pathogenic bacteria in the bowel (The State Serum Institute).

The rectal mucosa (15 cm) was swollen everywhere nobbly, bright red, haemorrhagic in parts.

X-ray of colon on March 2nd: The emulsion entered easily. The intestine was extremely pathologic with almost complete absence of haustra. Evacuation showed the mucosa greatly changed into coarse, oedematous, longitudinal folds. On admission the patient was given apple diet for 2 days, on Feb. 19th—20th again apples for 2 days. As long as nothing but apples was given, stools remained semi-solid, but on other food diarrhoea again set in spite of administration of Bis. Sal. (2 grs 4 times daily). Chemotherapy was now commenced, 1 g 6 times daily (60 grs in all) in the period from Feb. 24th to Mar. 6th having been given. Administration of Bis. Sal. was discontinued at the same time. During treatment with Salazopyrin semi-solid stools were passed 4—5 times a day. After this treatment had been discontinued, enemas were given of

|                                    |                                   |
|------------------------------------|-----------------------------------|
| Calcii carbonatis praecipitat..... | 50 grammes                        |
| Mucilag. gummi arabici .....       | 100 "                             |
| Aqua .....                         | ad 500 cm <sup>3</sup>            |
|                                    | (250 cm <sup>3</sup> every night) |

and, orally, pulvis calcis bismuthicus and ascorbic acid. The patient's condition improved gradually. From Mar. 24th she passed semi-solid stools twice a day only, from Apr. 4th solid stools containing neither mucus nor blood once a day. The weight increased to 62.2 kilos. The ascorbic acid in the serum rose to 1.12 mgs per 100 cm<sup>3</sup>.



X-ray on Apr. 14th showed considerable improvement of the colon, as the haustra, which had been almost completely absent in the transverse and descending colon, were now much more pronounced. If the pictures had not previously shown abnormalities, they would now have been regarded as normal. On her discharge the patient felt well.

**Case 6.** P. A. J. 33-year old female. (722/1942). Admitted April 8th. Discharged May 23rd 1942.

No previous major illness.

From the beginning of 1941 the patient had passed loose, mucous, haemorrhagic stools, for which she had received treatment in the surgical department of the hospital from June 7th to July 10th 1941.

On her admission the rectal mucosa as far as 20 cm was bright red, leathery, and much covered with mucus. On her discharge the mucosa was almost normal.

From Jan. 1942 her condition became aggravated with loose evacuations several times a day, sometimes blood and mucus only being passed. Temperature: Normal. The patient had lost weight (maximum weight: 70 kilos).

Physical examination: Nothing abnormal.

General condition: Good.

Height 162 cm. Weight: 61 kilos. Hmgb. percentage: 102. Sedimentation rate of red blood corpuscles: 11 mm/1 hour. Ascorbic acid in serum: 0.40 mgs per 100 cm<sup>3</sup>.

Ewald's test meal (1 hour): 35 + 28 well digested ÷ mucus. Kongo figure: 56.

Phenolphthalein: 70.

|                        |     |    |    |    |    |    |    |    |    |    |
|------------------------|-----|----|----|----|----|----|----|----|----|----|
| Blood (benzidine test) | 9/4 | 11 | 12 | 16 | 17 | 19 | 21 | 23 | 27 | 28 |
| Faeces:                | +   | +  | +  | +  | +  | +  | ÷  | ÷  | +  | ÷  |
| Catalase figures       |     |    |    |    |    |    |    |    | 20 | 10 |

Rectal examination April 10th (25 cm). In the lower part of the intestine the mucosa was swollen, bright red, covered with mucus. About 7 cm up there was a pea-sized polypus on the posterior wall. Further up the changes became less pronounced, but pus, mucus and blood passed down from the above intestine.

X-ray examination of the colon on April 13th revealed nothing abnormal.

On admission the patient had 1 solid evacuation per day. She was given a light diet and from Apr. 14th chemotherapy in the following manner:

|                     |             |     |        |         |       |       |
|---------------------|-------------|-----|--------|---------|-------|-------|
| Apr. 14th—Apr. 15th | Salazopyrin | 1   | gramme | 6       | times | daily |
| » 16th— » 20th      | »           | 0.5 | »      | 6       | »     | »     |
| » 21st— » 22nd      | »           | 0.5 | »      | 3       | »     | »     |
| » 23rd—May 14th     | »           | 0.5 | »      | 2       | »     | »     |
|                     |             |     | (51    | grammes | in    | all)  |

X-ray examination on April 22nd: Conditions on the whole unchanged.

Rectal mucosa: April 22nd: Unchanged.

May 20th: Only slight changes in the lowest part of the intestine. In the upper part the mucosa was still red and swollen.

**Case 8.** A. S. O. 66-year old female (808/1942). Admitted May 3rd, 1942. Discharged June 10th, 1942.

In 1923 the patient had been treated for abdominal trouble diagnosed as gall-stones, in 1928 for gastric ulcer. On the latter occasion she was said to have had haematemesis. Otherwise no previous major illness.

For the last 2—3 years the evacuations had been irregular, alternating between constipation (2—3 days) and diarrhoea (3—4 days). There had been no diarrhoea since November. In the periods with diarrhoea stools had been passed 5—6 times a day. Otherwise no dyspeptic symptoms and no loss of weight.

On Apr. 29th, May 1st, and May 3rd the patient had sudden pains round the umbilicus and in the left side of the abdomen and was therefore admitted to the surgical department with the diagnose subileus, cancer of the colon? Transferred to the medical department on May 8th.

Physical examination: Nothing abnormal.

General condition: Good. Temperature: Normal.

Height: 153 cm. Weight: 65.4 kilos. Hmgb percentage: 92. Sedimentation rate: 20 mm/1 hour. Ascorbic acid in serum: 0.16 mgs per 100 cm<sup>3</sup>.

Ewald's test meal (70 Min.): 21 + 5 cm<sup>3</sup> well digested + mucus. Kongo figure: 38 Phenolphthalein: 61.

|                 |                         |     |   |   |    |    |    |    |    |
|-----------------|-------------------------|-----|---|---|----|----|----|----|----|
|                 | Blood (benzidine test), | 4/5 | 5 | 6 | 10 | 11 | 12 | 14 | 15 |
| Faeces:         |                         | +   | + | + | ÷  | ÷  | ÷  | ÷  | ÷  |
| Catalase figure |                         |     |   |   | 20 | 30 | 10 | 35 | 25 |

Blood picture: Nothing abnormal.

Rectal mucosa (18 cms): Nothing abnormal.

X-ray examination of the colon (May 6th): The emulsion entered easily and quickly filling the colon completely. The latter was distinctly changed, the whole descending and most of the transverse part being seen as a rigid tube with complete absence of haustra; only the ascending colon and the hepatic flexure showed normal outlines. After evacuation the descending colon was highly contracted.

The patient was at first given a light diet and from May 19th full diet with certain exceptions. No dyspeptic symptoms were found. Twice a day the patient passed stools, as a rule solid but occasionally semi-solid.

On May 15th chemotherapy was instituted in the following manner.

|              |      |              |     |        |   |       |       |
|--------------|------|--------------|-----|--------|---|-------|-------|
| May 15th—May | 18th | Salazopyrin. | 1   | gramme | 6 | times | daily |
| » 19th—»     | 22nd | »            | 1   | »      | 3 | »     | »     |
| » 23rd—»     | 25th | »            | 0.5 | »      | 3 | »     | »     |
| » 26th—June  | 10th | »            | 0.5 | »      | 2 | »     | »     |

(55.5 grs in all).

X-ray control (June 6th) of colon after enema showed that although the haustra were still smaller than normal, they were much more pronounced than before particularly after emptying. Numerous small diverticula were also found both in the transverse and the descending colon.

On June 10th the patient was discharged, but treatment with Salazopyrin was to be continued at home.

**Case 9.** M. H. 24-year old female. Admitted May 27th, 1942.

No previous major illness.

After a confinement on April 23rd the patient had suffered from diarrhoea, mucous, haemorrhagic stools being passed up to 10 times a day. There were frequent attacks of rectal tenesmi, pains in the abdomen, nausea, vomiting, and during the last week before admission, rise in temperature to 39.8°C. Physical examination: The patient was rather worn out, but apart from some diffuse tenderness of the abdomen nothing abnormal was found. Her nutritional condition was below average. Height and weight: Not measured. Hmgb. percentage: 69. Sedimentation rate: 43 mm/1 hour. Urine + albumen ( $<0.1\%$ ). Microscopic examination: Nothing abnormal. Erythrocytes: 3.81 millions. Colour index: 0.90.

Leucocytes: 12,000. Icteric index: 4. Blood film: Nothing abnormal.

Widal test:  $\div$ . Ascorbic acid in serum: 0.08 mgs per 100 cm<sup>3</sup>.

Ewald's test meal (1 hour): 25 + 15 cm<sup>3</sup>, well digested without mucus.

Kongo figure: 50. Phenolphthalein: 65.

|                 | May 27th | 28th | 29th |
|-----------------|----------|------|------|
| Blood           | +++      | ++++ | +++  |
| Faeces: Mucus   | +        | +    | +    |
| Catalase figure | 55       | 45   | 50   |

Rectal examination in proctoscope: Mucosa swollen, bright red, haemorrhagic when touched. Temperature: Irregular (38.6—40.1° C. in the evening, 38.1—36.9° C. in the morning).

X-ray examination of the colon: The emulsion entered easily completely filling the colon, with no stops or defects in the contrast. The outlines of the colon appeared somewhat irregular which circumstance indicated coarse folds in the mucosa with an ample secretion of mucus. The haustra were also rather irregular and coarse. Otherwise nothing abnormal was found.

On her admission the patient passed loose stools containing much blood and mucus 7—9 times a day, and as this condition was quite unaffected by the apple diet 1 gramme of Salazopyrin was administered 6 times daily (59 grs in all) from May 29th to June 8th. Then the treatment had to be given up, as it was impossible for the patient to take any more on account of nausea. The treatment had had no demonstrable effect, as the patient continued to pass loose stools with blood and mucus 6 times a day, the temperature was still high, and the hmgb. percentage had fallen to 48.

### Discussion.

When considering the results of the above therapy we noticed that they varied considerably in the different cases. It was not possible to say beforehand which patients were suitable for treatment and which were not.

The most striking result was obtained in Case 3, an 11-year old boy, who had suffered from diarrhoea since infancy. On admission he was in a poor condition, emaciated and slightly febrile, there was a tendency to epistaxis, and a light attack of tetany occurred as a consequence of hypocalcemia. The patient also suffered from chronic tonsillitis accompanied by frequent rises in temperature and articular pains. Administration of M & B 693 (28.25 grs) immediately caused radical improvement, but the stools continued to be semi-solid. Salazopyrin (95.75 grs) was administered. Stools now became quite normal and have remained so during 7 months of observation. The subjective condition of the patient became satisfactory.

A satisfactory effect of the treatment was also seen in Case 7, where 108 grammes of Salazopyrin were given. The diarrhoea stopped, and the changes in the rectal mucosa decreased considerably, even they did not disappear entirely.

Cases 1 and 5 also presented excellent results (they received 28 grs. M & B 693 and 60 grs. Salazopyrin respectively). At the time of the discharge of Case 1 it was still necessary to administer Bis. Sal., stools were semi-solid, and changes, although slight, were still seen in the rectal mucosa. In Case 5 the patient passed normal stools at the time of her discharge. In neither case, however, did the improvement set in during chemotherapy, but gradually after its discontinuation, and while other treatment was being given. For this reason it is difficult to judge how great a share the chemotherapy had in the results obtained.

In Case 6 (51 grs of Salazopyrin) treatment was instituted during a period when the patient's stools were normal. She presented a considerable improvement of the rectal mucosa.

In Case 8 (55.5 grammes of Salazopyrin) the patient did not suffer from diarrhoea, and therefore the effect of the treatment

manifested itself chiefly by the X-ray examination, which revealed a considerably improved condition of the bowel.

Case 9 (59 grammes of Salazopyrin): The treatment had no effect whatever.

Case 2: After administration of M & B 693 (6 grs) + Sulphamethylthiazol (12 grs) the condition of the patient was definitely aggravated and remained so during her stay ( $> 1$  year). By treatment with Salazopyrin (120 grs) at a later date an insignificant, slight improvement was noticed.

Finally, in Case 4 treatment had to be discontinued after 6 grs of Sulphamethylthiazol, as the patient showed intolerance towards the preparation. A year later the mucosa of the intestine was found to be normal, but it cannot be supposed that the improvement was due to Sulphamethylthiazol.

As the available data are too few for grouping, the preparations used cannot be evaluated in this manner. But it must be stressed that the cases in which more than one preparation have been used, for example Case 3, have given the impression that Salazopyrin was the most effective. Moreover, as our experience of chemotherapy has grown, we have come to the conclusion that in a number of cases we stopped the administration too soon, and that a better result might have been obtained by a more prolonged treatment.

The X-ray examinations were particularly valuable for the evaluation of the therapeutic results, as the conditions revealed by X-ray not always fulfilled our expectations as judged from the subjective condition of the patient.

In two cases (1 & 4) there was no X-ray examination. In Case 6 nothing pathologic was found. In cases 2 and 9 chemotherapy was of no effect. The remaining four cases showed the following:

In Case 5 the considerable röntgenologic changes had almost disappeared at the time when the stools became normal and the subjective condition of the patient good. The rapid disappearance of the röntgenological changes indicates that no deep anatomical changes were present, which is consistent with the short duration of the illness, but that the main pathologic changes were easily reversible, as for example oedema and hyperaemia.

Quite conversely, an excellent effect on the diarrhoea was

observed in Cases 7 and 3 at a time when very pronounced roentgenological changes still existed. This was particularly noticeable in Case 3, where the patient already on the first day after administration of Salazopyrin passed normal stools, which remained so for 7 months, and the patient felt well, although the X-ray showed very little improvement compared with the previous year. Evidently, this incomplete anatomical cure explains the circumstance emphasised by Öhnell (3) that not a few patients who had been successfully treated shortly afterwards had a relapse. A good deal of reservation must therefore be used when calling a patient cured on basis of the stools, unless there is an X-ray control at the same time.

Lastly, Case 8 is interesting, as there is a good improvement of the X-ray picture, though stools were fairly normal at the beginning and did not change during the treatment. From this may be concluded that chemotherapy may also be of effect in cases without diarrhoea. The same may be seen in Case 6.

### Summary.

1) 9 cases of severe colitis and proctitis, which were treated chemotherapeutically with Salazopyrin, Sulphamethylthiazol and M & B 693 (together with our usual dietetic and medication treatment) are recorded.

2) Therapeutical results: 1 case practically cured, but the cure cannot with certainty be attributed to chemotherapy. 5 cases improved, but in 1 of them the improvement cannot be definitely due to chemotherapy.

1 case was unaffected.

1 case was aggravated.

In 1 case treatment had to be discontinued on account of intoxication.

3) The patient may subjectively feel completely well, and the stools be normal for months, even though pronounced changes are still revealed by X-ray examination. For this reason X-ray control is absolutely necessary for the establishment of a cure.

4) The effect of chemotherapeutic preparations are not limited to patients with diarrhoea, but even in cases in which stools are normal to begin with an improvement may be seen in the rectal mucosa and on the X-ray.

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(From the Departments of Pathology and Internal Medicine of the State University, Leyden, The Netherlands).

## Aspiration-biopsy of the Liver in Mononucleosis infectiosa and in Besnier-Boeck-Schaumann's disease.

By

CORNELIA van BEEK and A. J. CH. HAEX.

(Submitted for publication October 19, 1942).

Bingel(1) and his assistant Olivet(2) in 1923, and again in 1926, pointed out the importance of liver puncture to diagnosis and treatment. The material on which they based their indications and contra-indications covered 140 cases. The column of parenchymatous tissue obtained by the puncture, was fixed, embedded, cut and stained in the usual way. Although their results proved that a useful method of assistance in the diagnosis of liver diseases had been found, it was completely forgotten. In 1939 however the procedure was rediscovered: for this we are indebted to the American Baron (3) and especially to the Danes Iversen and Roholm(4).

Using the technique of the two last-named authors one of us (Haex) performed more than 200 punctures of the liver in cases showing symptomatically a widely divergent character. In none of the patients the operation caused any lasting injury, and in two cases only did we see a peritoneal reaction: these two patients were suffering from cholangiolitis. In both cases large masses of coli bacilli were grown from the tissue obtained by the aspiration. Therefore, it should be borne in mind that in cases of icterus accompanied by fever, and when coli bacilli are present in the duodenal fluid, liver puncture is always risky, and should perhaps



better be avoided. The puncture failed but very rarely, and in contradiction to the finding of Baron (3) and Fiessinger (5) it succeeded quite well in cirrhotic livers. As a control of the clinical diagnosis the method has yielded valuable results, and by the aid of it the presence of leucemia, cirrhosis, or amyloidosis could be confirmed or excluded. Twice a cancer metastasis was found, but this was more or less a question of chance, and if no metastases are met with, it does not mean that none are present.

One half of the column of parenchymatous tissue was fixed in 4 per cent formalin; the other half in 96 per cent alcohol. In order to obtain an impression of the amount of glycogen present in various kinds of liver diseases, the tissue fixed in alcohol was stained by the aid of Best's method.

A remarkable result of this investigation was that tissue of a normal living liver fixed in formalin does not show a trabecular but a mosaic structure, the cells being polygonal, sharply outlined and poor in protoplasm. This must be due to the presence of a large amount (6—8 g per cent) of glycogen. Owing to a loss of glycogen in the last days of life and during the agony, the liver obtains the well-known trabecular structure which it shows at autopsy. The latter, therefore, must be regarded as pathological.

In the course of our work we came to the conclusion that the greater part of the specimen should be used for micro-glycogen-determinations. The results of these determinations, which will be fully described in another paper, were compared with those obtained by the aid of the slides stained with Best's method. There appeared to be complete parallelism between the two, and, as Nielsen, Okkels and Stockholm-Borresen (6) had found already in 1932 for dogs and guinea pigs, an estimation of the glycogen content by the aid of the slides is therefore practicable.

In liver diseases of a most divergent nature the glycogen content of the liver was found to be normal. Exceptions were Basedow's disease, adenoma of the islets of Langerhans and subacute atrophy of the liver, for here the slides stained according to Best as well as the quantitative micro-determination showed an unmistakable decrease of the glycogen content. This is in agreement with, and at the same time an extension of, the results obtained by Krarup (7), who worked with slides stained according to Best, and found the amount of glycogen in cases of hepatitis epidemica, obstructive jaundice and

cirrhosis unchanged. In a case of acute yellow atrophy of the liver practically no glycogen was found by him. Nuclear glycogen we recognized to be present in about 25 per cent of our cases; the finest slides were obtained from a patient who proved to have cancer



Fig. 1.

Glycogen staining according to Best.

In the nuclei sharply defined glycogen globules are seen. ( $\times 400$ ).

metastases in the liver (fig. 1). Nuclear glycogen is usually taken to be present in cells that are poor in plasma glycogen [Askanazy and Hübschmann (8); Klestadt (9)]. On the whole this appeared to be true; occasionally, however, we found it also in cells that were rich in glycogen.

The foregoing survey of liver biopsy in general is intended as an introduction to a discussion of the pathological changes of the liver occurring in two diseases (mononucleosis infectiosa and Besnier-Boeck-Schaumann's disease) which may be classified with the reticulo-endothelial affections. This is a group of diseases in which pathological changes of the reticulo-endothelial system form the most prominent symptom. With regard to diseases like typhoid

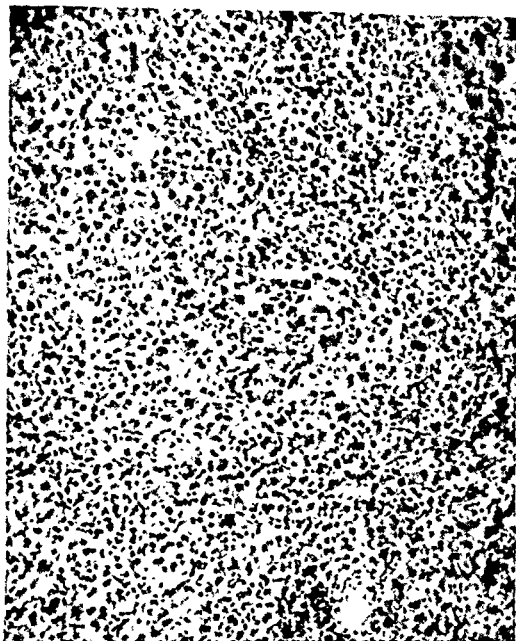


Fig. 2.]

Mononucleosis infectiosa. 'Seen under a low power the aspect is like that of myeloid leucemia. ( $\times 100$ ).

fever, lues, tuberculosis, malaria etc. it is still an open question whether they should be placed in this group or whether they are better left in the group of infectious diseases. Mononucleosis infectiosa [Du Bois (10) and van der Zwaag (11)] and Besnier-Boeck-Schaumann's disease [Sézary (19)] at any rate have by various authors been referred to this group. The etiology of these diseases has not yet been fully elucidated. Sézary (19) placed them in a subdivision which he calls «réticuloses hyperplasiques».

In mononucleosis infectiosa the blood contains a peculiar kind of monocytes, which have been regarded as stimulated reticulum cells.

In the peripheral blood they have sometimes been found in exceedingly great numbers, the differential counts of blood smears revealing values of 90 per cent and more. The enlargement of spleen, liver and lymphatic glands in combination with the presence in the blood of these monocytes, would indicate a disease of the reticulo-endothelial system. In the group of the reticulo-endothelioses this

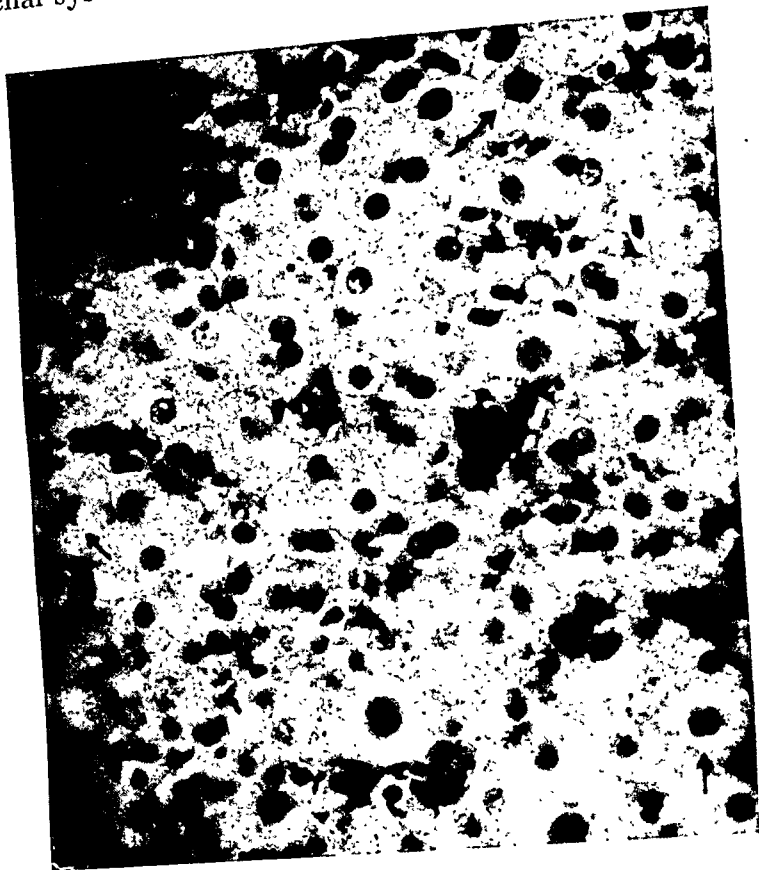


Fig. 3.  
Mononucleosis infectiosa. Three liver cells are in the act of mitosis.  
( $\times 400$ ).

affection might find a place as an acute form [according to Sézary (19): «évolution rapide»).

In the literature we had at our disposal we did not find records of liver changes in mononucleosis infectiosa. As the patients as a rule recover, but few obductions have been made, and these apparently revealed no conspicuous changes in the liver. However, as mononucleosis infectiosa is regarded by some authors [Du Bois (10), van der Zwaag (11)] as a disturbance of the reticulo-endothelial system,

and as it may even be accompanied by icterus [Bruins Slot (12)], it seemed likely to us that nevertheless changes might be present. We had the opportunity to study a male patient of 24, who showed a positive Paul-Bunnell reaction (1/224) and the following blood formula: eosinophils 0; stab cells 5 per cent; segmented forms 7 per

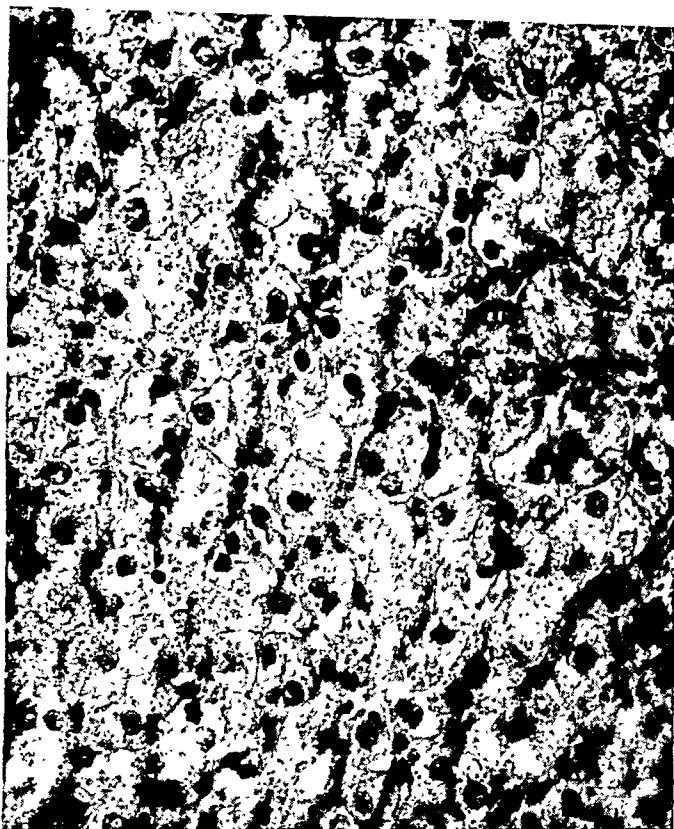


Fig. 4.

Mononucleosis infectiosa. Three and a half weeks after the first puncture the liver tissue is once more practically normal. ( $\times 400$ ).

cent; monocytes and lymphocytes 88 per cent; total number of leucocytes: 9700. Fourteen days after he fell ill, a liver puncture was performed, which revealed a quite peculiar condition of the tissue. Especially when seen under a low power it reminded one of myeloid leucemia (fig. 2). More strongly magnified the liver cells appeared to be interspersed with numerous monocytoïds and some polymorphonuclear leucocytes. The number of mitoses was considerable, but it was impossible to make out whether the dividing cells still

belonged to the wall or were already suspended in the blood stream. Mitoses were also observed in the liver cells themselves, which contained but a moderate amount of glycogen (fig. 3). The triangles of Kiernan were rich in cells and contained numerous lymphocytes. After 3 1/2 weeks, when the patient was up again, another puncture was made, which revealed a practically normal

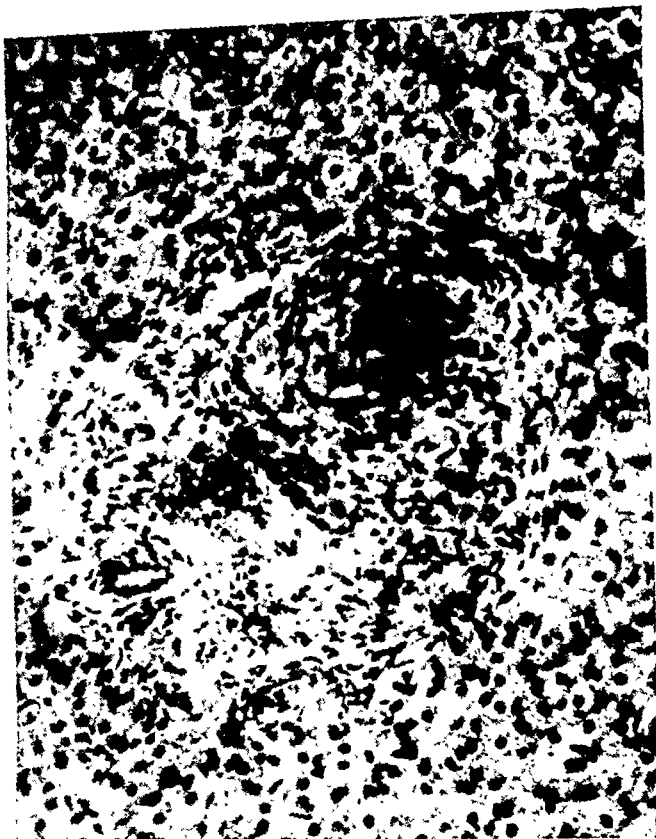


Fig. 5.

Besnier-Boeck-Schaumann's disease. Triangle of Kiernan, in which a submiliary tubercle containing a giant cell may be seen. ( $\times 200$ ).

condition of the liver tissue (fig. 4), the only abnormality being that the triangles of Kiernan were still rich in lymphocytes. A relative lymphocytosis was still present (45 per cent).

The second disease studied by us was that of Besnier-Boeck-Schaumann, S  zary (19) regards this as a »r  ticulose hyperplasique;   volution chronique«.

On four patients, whose disease on clinical as well as on r  ntgenological grounds had been diagnosed as that of Besnier-Boeck-

Schaumann, a liver puncture could be performed. Two of the punctates showed submiliary, non-caseous epitheloid tubercles, which were sometimes bounded by lymphocytes, and which occasionally contained a giant cell. In one of these patients, a 19 year old lad, these foci were confined to the triangles of Kiernan (fig. 5), whereas in the other patient, a girl of 18, the foci lay mainly in the paren-

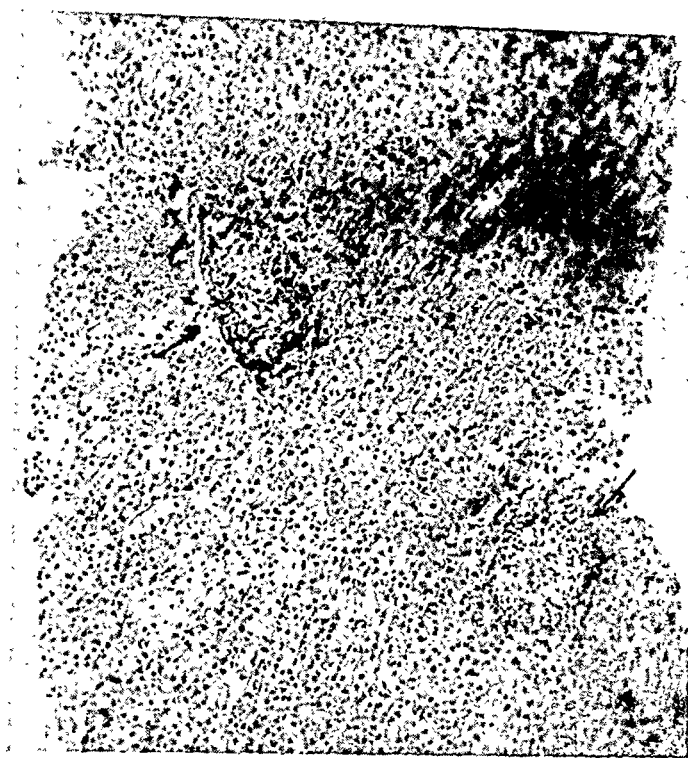


Fig. 6.

Besnier-Boeck-Schaumann's disease. Embedded in the parenchyma two submiliary tubercles are found. ( $\times 70$ ).

chyma (fig. 6), though in the triangles too they were not completely absent. In the specimens of the two remaining patients the microscopical assay revealed no abnormality.

The observation made by Nickerson (13) at autopsy, that in the case of the disease of Besnier-Boeck-Schaumann the liver is usually affected, is corroborated by our findings. Nickerson found in five of his six cases the above described foci; mostly they occurred in the portal connective tissue, but in the lobules themselves too they were sometimes met with. Of patients suffering from this disease too but

few obductions are known, as the disease has but rarely a fatal issue. Where pathological changes of the liver are mentioned, definite information with regard to the whereabouts of the foci often fails, but the communications of von Gebssattel (14), Deelman (15), Schaumann (16), Nickerson (13), Cotter (17) and Hollister and Harrell (18) show that dissemination preferably takes place towards the triangles of Kiernan.

### Summary.

The microscopical aspect of liver tissue obtained by puncture from the living organ and fixed immediately, is described.

The normal liver does not show a trabecular, but owing to the presence of a large amount of glycogen, a mosaic structure. A decrease of the glycogen content is in the diseased liver but rarely observed. It was seen only in Basedow's disease, adenoma of the islets of Langerhans and subacute atrophy of the liver. In 25 per cent of the cases nuclear glycogen was met with.

Mononucleosis infectiosa is an affection of the reticulo-endothelial system. In a patient suffering from this disease a proliferation of monocytoïd cells was found in the midst of the liver cells, which themselves also showed mitoses. The microscopical aspect resembled that presented by myeloid leucemia. After 3 ½ weeks the tissue had regained its normal condition.

In the disease of Besnier-Boeck-Schaumann submiliar, non caseous, epitheloid tubercles are met with. They occur mainly in the triangles of Kiernan.

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(From the Children's Sanatorium »Hoog-Blaricum«, director dr. G. J. Huët, The Netherlands).

## Chronic miliary tuberculosis.

By

S. van CREVELD and G. J. HUËT.

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### 1. Introduction.

According to current conceptions, the arise of a miliary tuberculosis depends on some conditions, the most important of which are: the presence of tubercle bacilli in a sufficient number in the blood stream, the virulence of these bacilli, and further the way in which the individual reacts upon his infection with tuberculosis. Miliary tuberculosis may become manifest in every stade of a tuberculosis, but experience has shown that most cases of miliary tuberculosis occur in early youth and more especially during the first year of life. Next to this also the age of puberty brings forth an increased predisposition. Besides, with the extension of the radiographical examination it has appeared that development, course and duration of a miliary tuberculosis may show great variety. Based on these facts a classification has been made in acute, subacute and chronic miliary tuberculosis, and especially of late experience has learnt that these chronic cases may pass on to recovery.

In recent years the problem of chronic miliary tuberculosis has greatly drawn the attention of many investigators. Especially two questions have been plated in the foreground: does chronic miliary tuberculosis really exist and if so, in which way origin, course and eventual healing can be explained? And secondly: how can this chronic miliary tuberculosis be diagnosed? — In this article we

want to discuss these questions on the base of a number of observations of our own, and we will enter more especially into the different possibilities of explaining the arise of chronic miliary tuberculosis.

*2. Differentiation from non-tuberculous conditions in which the radiograph of the lungs also shows many minute spots.*

Whereas the diagnosis of acute miliary tuberculosis is based on definite pathological findings, that of chronic miliary dissemination is often made on relatively loose grounds. This namely often happens when in a patient with positive tuberculin tests the radiograph of the lungs shows many diffusely spread small spots. However, in such cases first of all one has to distinguish clearly from other conditions in which the radiograph of the lungs also shows many minute spots. A number of these conditions usually can be differentiated rather easily from miliary tuberculosis; so for instance miliary carcinosis, coniosis, multiple pyaemic small abscesses, leukemic infiltrates of miliary form, disseminated influenza-pneumonias, definite forms of lymphogranuloma, definite storage-diseases and bilharziosis of the lungs. Of late this series has been enlarged by two other diseases in which the radiograph of the lungs also greatly suggests miliary tuberculosis: in the first place the idiopathic progressive brown induration of the lung (Glanzmann) where the spots, visible in the radiograph, are due to a marked hemosiderosis of the lungs as a consequence of recurring slight and large hemorrhages. The second disease is the diffuse myomatosis or fibrosis of the lung with formation of cysts (compare a. o. Rosendal). The relatively small number of cases of this last mentioned disease, described till yet, partly shows relation to tuberous sclerosis. In this affection the cysts may be invisible in an ordinary radiograph (but clearly visible in a tomographic picture; compare a. o. de Fine Licht), so that radiographically there may exist a great resemblance to miliary tuberculosis. However, as a rule also the differentiation of miliary tuberculosis from these two diseases is not difficult, but other diseases often offer greater difficulties in this respect, such as pulmonary congestion, Besnier-Boeck's disease and tuberculous bronchopneumonia with confluating foci. Especially the distinction from Besnier-Boeck's disease may give rise to great difficulties. As a fact there exists a series of criterions which eventu-

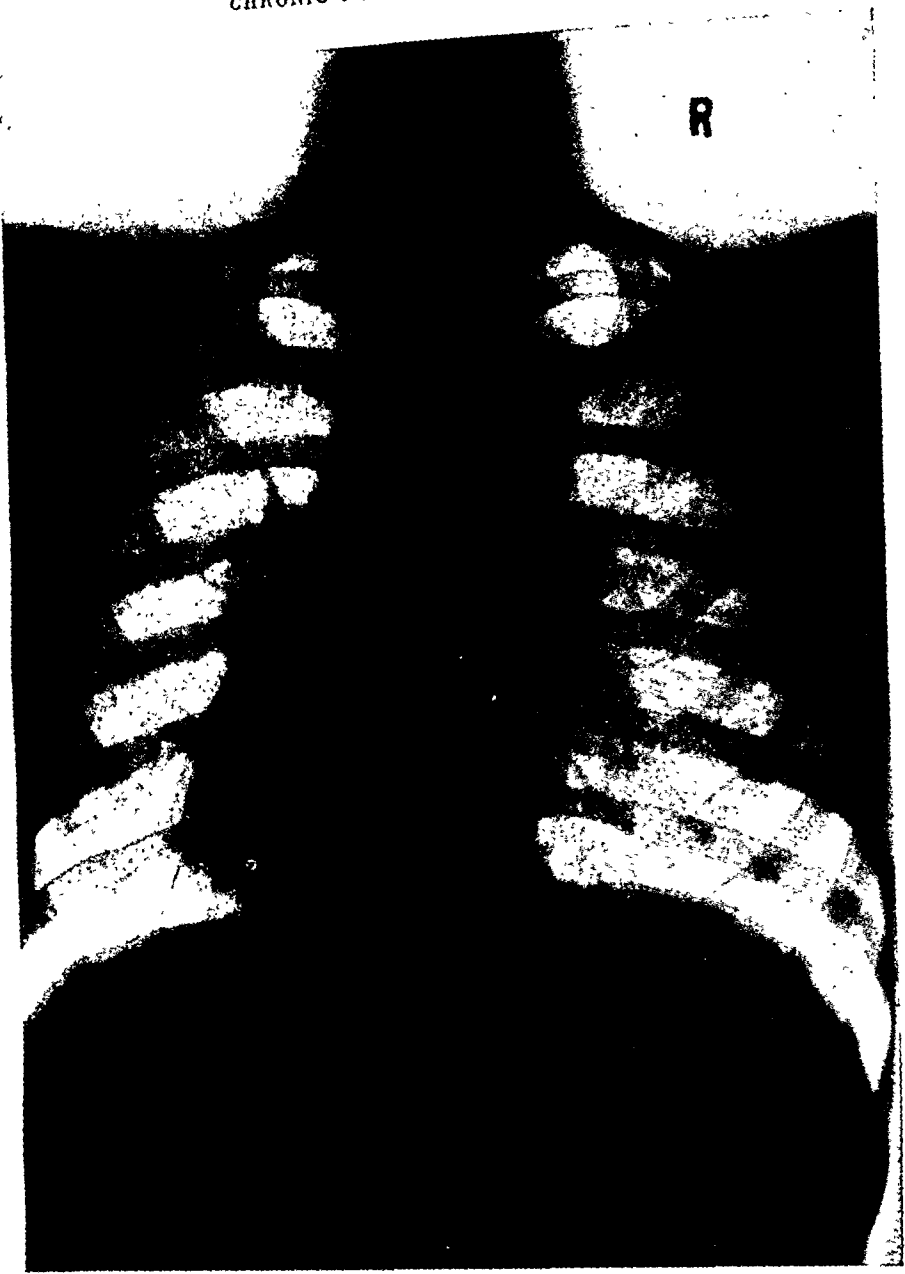


Fig. 1. Radiograph of the lungs in a case of Besnier-Boeck's disease: typical broadened hilar shadows, reticular pattern in both lungs.

ally can be used in differentiating between this disease and chronic miliary tuberculosis: negative tuberculin tests, typical broadened hilar glands, on the radiograph of the lungs usually a more reticular than spotted pattern of the foci<sup>1</sup> (compare fig. 1), more or less

<sup>1</sup> The broadening of the hilar gland may be absent, but notwithstanding this the reticular pattern may be so typical that it justifies the diagnosis of Besnier-Boeck's disease.

typical localization of bone cysts, deviations in the protein spectrum, increased calcium content of the serum, renal calculi (compare a. o. van Creveld). However, in other cases the differentiation remains difficult; this holds true a. o. also for the course of deviations visible in the radiograph, for just as in chronic miliary tuberculosis also in Besnier-Boeck's disease the deviations of the lungs may totally disappear. There exists a legitimate hope that the differential diagnosis between Besnier-Boeck's disease and chronic miliary tuberculosis in such dubious cases will be facilitated by the discovery of Kveim in Oslo. This author has described a skin reaction which is performed by means of an extract of a lymphgland, removed from a patient suffering from Besnier-Boeck's disease in the active stade. The reaction should have a specific character (compare also a. o. the discussion-remarks of Lomholt and van Dale).

### *3. Criteria for the diagnosis of chronic miliary tuberculosis.*

In connection to the above mentioned facts it appears to be necessary that the diagnosis of chronic miliary tuberculosis should be submitted to severe criteria, which should be fulfilled as much as possible. These criteria are:

1. positive tuberculin tests.
2. eventual certainty that there has existed a contact infection.
3. if possible presence of tubercle bacilli in the gastric lavage or in the sputum.

With a view to the conclusive force for the hematogenous genesis it is necessary, that the following conditions should be fulfilled as much as possible:

1. the presence of such foci outside the lungs as only can arise by hematogenous dissemination: i. e. foci in bones or joints, in lymphglands, skin, kidney, eye, spleen and liver. To these are also belonging calcified foci in liver and spleen, which during life have been established radiographically (compare a. o. Courtin and Duken, Hellgren, Duken, and Plieninger).

Wallgren has found highly pronounced calcification in the spleen in one case which came to autopsy and he also points to the fact that these calcified foci undoubtedly might have been established during life. In one of the cases reported upon by Klingenstein the removed spleen appeared to contain, next to caseated, also calcified tubercles.

2. *regular* spreading of the small foci in both lungs.

3. the presence of *small* foci of about the same size. However, on this rule there are exceptions which nevertheless are due to a miliary dissemination (compare later on the second case on which we report).

In order to get an opinion about the way in which a case of miliary tuberculosis eventually has developed, it is of importance to consider the following facts.

1. The presence whether or not of factors indicating a restricted dissemination (monoarticular or multiple foci of the bones, the intact condition of the kidneys, the failing of swelling of the spleen, of meningitis etc.) Here we have to remark, however, that not rarely a miliary tuberculosis occurs with localization of tubercles in organs of great vital importance (kidneys, chorioidea), which takes a chronic and frequently favourable course.

In the case of Ladenius, described in the thesis of Duyster, a boy, aged 15 years, suffered from miliary dissemination in the lungs, a bilateral kidney- and a bladder-tuberculosis, gonitis tuberculosa, tuberculosis of one drum of the ear, while in the fundus oculi first one, later on a second tubercle could be found. Nevertheless, the boy still proved to be in good condition 5  $\frac{1}{2}$  years after the first examination.

In this connection we must also mention the observation of Opie and Anderson concerning a case in which not only liver, lungs and spleen proved to be interlarded with calcified small nodules, but where also a number of calcified nodules were found on the pia mater over the frontal lobes of the brains.

2. The localization of the metastases and the succession in which these metastases and the miliary dissemination in the lungs occur. Further on in this article we shall give a nearer discussion of this point.

3. The presence whether or not of arguments speaking in favour of the benignity of the infection (as such may count a. o. a combination with lupus or the presence of papulo-necrotic foci).

4. The final stade of the disease: does there exist a complete resorption of the foci of the lungs — which points to a rather non-specific exsudative process — or a calcification, which is more in favour of a specific process. — However, we must directly remark here that even when such sharply defined bounds are drawn, the cases still mutually may show great differences. Not rarely we see in the literature that also such cases are reckoned among those of

chronic miliary tuberculosis in which during the course of the disease cavernous processes or a confluent tuberculosis occurred. The genesis of these complications is very intricate however, and for this reason we think it advisable to leave the cases with such a course out of account.

#### 4. *Cases observed in the Children's Sanatorium »Hoog-Blaricum«.*

All cases of chronic miliary tuberculosis on which we report here, are children who have been nursed during a long time in the Children's Sanatorium »Hoog-Blaricum« (Holland). Most children have shown during the course of the disease distinct extra-pulmonal tuberculous lesions which only can be explained by a spreading of tubercle bacilli by way of the blood stream. This in itself may be considered as an argument in favour of the conception that also the symptoms of miliary tuberculosis of the lungs in these cases must be explained by a dissemination of tubercle bacilli along the blood stream.

**Case 1.** This girl, when 3 years old, probably had an erythema nodosum. At the age of 4  $\frac{1}{2}$  years she got diphtheria, followed by paralyses. Shortly afterwards she complained of the right leg; the diagnosis of coxitis tuberculosa was made. At first she was treated with extension, later on a plasterbandage was applied. In the beginning of 1925, when 9  $\frac{1}{2}$  year old, she was nursed once more in a surgical department on account of the coxitis; after some time suspected symptoms of the lungs were found, so that she was transferred to an internal department. In April 1925 the radiograph of the lungs revealed that the surroundings of the right hilum were too much pronounced and especially in the right lower zone were several calcified foci. The left hilum showed a similar picture in a smaller degree. The Pirquet test was positive. No expectoration. The source of infection most probably was the mother.

In Sept. 1925 at the age of 10 years, she came to the Sanatorium in good general condition. The thyroid gland was distinctly palpable. At physical examination only very slight deviations were noticed in the lungs. The Pirquet test was positive. The radiographic examination of the lungs (Sept. 18, 1925) however showed a miliary dissemination in both lungs and a hilar infiltration at the right side. In the beginning the temperature was subfebrile, later on normal. On a radiograph of the beginning of Dec. 1925 it appeared, that the miliary spots had decreased. In the middle of Febr. 1926 the right hilum was dense and broad, in the right lower zone a calcified primary complex was seen, and the whole right side showed a slightly diffuse veiling. The miliary aspect of dissemination had completely disappeared. On the radiograph of the lungs, taken in the middle of Nov. 1926 a calcified primary focus was visible in the right lower zone and

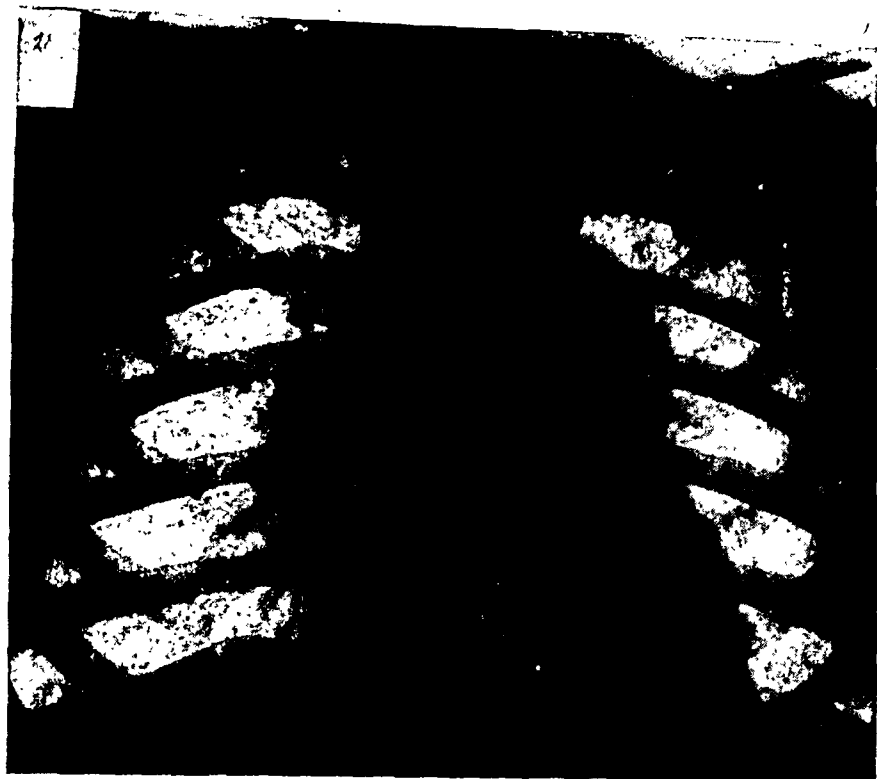


Fig. 2. Radiograph of the lungs in case 2 on admission: diffuse coarse mottling of both lungs with broadened hilar shadows.

regularly went to school. In June 1942 we learnt that she had remained in good condition and that also the thumb had not given rise to complaints.

**Case 3.** When admitted to the Sanatorium, in Jan. 1934, this boy was nearly 2 years old; the mother suffered from tuberculosis of the lungs. The disease of the child began after whooping cough; a radiograph of the lungs at the age of 1 ½ year showed at the right side a primary complex and further a hematogenous early dissemination («Frühstreuung» of the German authors) in both lungs. The tuberculin tests were positive; from the fasting stomach content tubercle bacilli could be cultivated. The spleen was enlarged, the temperature subfebrile.

On admission to the Sanatorium diffuse stenotic breath sounds could be heard over both lungs. The radiograph showed in the right lower zone a primary complex and further a diffuse dissemination in both lungs. Some months afterwards the child got a scrofuloderma on the abdominal wall. At that time the spleen was no more palpable; the temperature still was subfebrile. Half a year after admission the radiograph of the lungs showed in the right lower zone a calcified primary complex and further in right and left lung numerous lesions which clearly were about to calcify. Shortly afterwards the temperature became normal and remained so; in the sto-



much content tubercle bacilli could no longer be detected. The whole process had become inactive. In Febr. 1936 the boy was discharged.

Shortly afterwards, when the boy was nearly 4 years old, the radiograph of the lungs, especially in the right upper zone, showed many calcified spots; further a large calcified focus in the right lower zone and calcifications in both hili, at right more than at left. Six years afterwards the radiograph still was about the same, with the exception that the small calcified spots in the right upper zone and elsewhere had decreased in number. The boy had kept well. In Apr. 1942 the red cell sedimentation was normal.

**Case 4.** This girl, whose mother and brother have been nursed in a sanatorium, has been ailing since the age of 4 years; she often has fever, vomits a great deal and is very soon exhausted. When 6 years old, she is admitted to a children's hospital, where the diagnosis of pulmonary tuberculosis was made. The radiograph shows a diffuse dissemination with small foci in both lungs, further a pronounced hilar and at left probably also a paratracheal glandular swelling. She remained in the children's hospital during  $1\frac{1}{2}$  year and was discharged on account of whooping cough being introduced in that department. Then the girl went to school during 7 months, but she became ailing again and was very soon tired; only with great exertion was she able to sit in an upright position, which in the beginning was ascribed to her corpulency. However, examination showed the existence of a spondylitis, and she was laid in a plaster bed. In Aug. 1925, when about 9 years old, she was admitted to the Sanatorium on account of this spondylitis. The girl was very stout; the temperature subfebrile. At percussion and auscultation the lungs showed only small deviations. There was a pointed gibbus of thoracalis VII and VIII. The radiograph of the lungs revealed a hilar infiltration at the right side and further a bilateral paratracheal glandular swelling. In the lungs, especially in the left one and in the upper zone of the right one, a rather large number of fairly coarse lesions were present; the picture of a miliary dissemination had disappeared. The radiograph of the lungs, 2 months after admission, showed on both sides a rather pronounced hilar infiltration and a somewhat broadened mediastinum. For the rest the aspect of the lungs was fairly normal, apart from some small foci near the left hilum. Also on later radiographs of the lungs no distinct deviations could be found any more, apart from a slightly broadened mediastinum. — The spondylitis had given rise to a destruction of thor. VII and VIII, the remnants of which had grown together to a wedge.

The girl had remained very stout and small, but no endocrine cause could be detected for this fact, even not in 1940, when at the age of 23 years, an extensive clinical observation took place. Then her general condition, apart from the corpulency and small size, was good.

**Case 5.** When 3 years of age, this boy got high temperature and began to cough. At physical examination no deviations could be found, but on

the radiograph both lungs showed a mottled aspect with a hilar process on the left side. The spots greatly varied in size. The Pirquet test was positive. Two months later the high temperature decreased. The radiograph still showed the same picture with diffusely spread numerous smaller and coarser foci and at the left side a hilar process. — On admission to the Sanatorium, in Oct. 1925, the general condition was excellent; the boy then was 4 years old. The spleen was not palpable, the respiration frequent and superficial. Percussion revealed dullness over the left part of the thorax. At auscultation highly weakened breath sounds with bronchitic murmurs could be heard over the left side. Phlyctaenular conjunctivitis of the left eye. The temperature remained slightly elevated during the first months. The radiographs of both lungs showed numerous fine and coarser stippling. At the left side a dense shadow was visible from hilum to top. After a three months' stay in the Sanatorium the patient left the institute, contrary to the doctor's advice. One year and a half later the boy again was febrile, and now he had a coxitis. At admission to a hospital there was, moreover, again an extensive pulmonary process.

Two years after discharge from the Sanatorium the radiograph of the lungs revealed at the right side a fairly large number of calcified points and also many spots, at the left side an extensive pleural thickening. Another two years later the radiograph revealed at the right side still a relatively large number of calcified points, especially in the right upper zone, but no spots; at the left side the pleural thickening. Especially on account of the coxitis the patient had spent  $2\frac{1}{2}$  years in a sanatorium. — In Apr. 1942, when the patient was 20 years old, he lived at home, but walking caused great difficulties and he spends his life principally in a sitting position.

**Case 6.** In the spring of 1925 this boy, aged  $2\frac{1}{2}$  years, fell ill with fever and coughing fits; occasionally he also was dyspnoeic. Shortly afterwards he had many subcutaneous hemorrhages, but the number of thrombocytes was about normal and the bleeding time only slightly prolonged. The general condition was good; no fever. Occasionally phlyctaenular conjunctivitis. The Pirquet test was strongly positive. Examination of the lungs: on both sides many dry sibilant bronchitic murmurs and during a long time at the left side in the lower zone behind, there was shortened percussion with weakened breath sounds. The spleen was not palpable. The radiograph of the lungs at the age of 3 years showed the characteristic picture of a miliary tuberculosis with infiltration of the right hilum. In the right lung the ophthalmologist then suspected the presence of a rather large tubercle. These findings gave rise to an unfavourable prognosis, notwithstanding the good general condition of the patient. When however the radiograph of the lungs of some months later gave just the same picture, while the general condition also had remained as good as before, admission to a sanatorium was recommended.

This occurred in Nov. 1925, when the boy was  $3\frac{1}{3}$  years old. Physical examination of the thorax: at the left side the frontal part is rather dull;

on the sternum and behind bilateral dullness next to the spinal column. At the left side in front and behind weakened breath sounds. The spleen is not palpable. The Mantoux reaction is positive. The radiograph of the lungs reveals a miliary dissemination, which is more pronounced at right than at left. The diazo test is negative. — Half a year after admission the radiograph showed remnants of relatively numerous, fairly coarse foci and a dense right hilum. Another radiograph, taken 8 months later, showed a displacement of the heart to the left; miliary lesions no longer were visible. At the left side in front and in the middle was a diffuse veiling. Another 2 months later, when the boy was nearly 5 years old, the radiograph showed a displacement of heart and mediastinum to the left, and on the right side the pattern was much more pronounced than at the left one. During the stay in the Sanatorium the temperature was normal to subfebrile, apart from a short period with tops to more than 40° C.

At discharge from the Sanatorium, when the boy was nearly 5 years old, the left side of the thorax was somewhat flatter than the right and showed a rather marked dullness at percussion with weakened breath sounds. — At the age of 11 years the only complaint consisted in a slight cough, and the boy easily became dyspnoeic. No tubercle bacilli in the sputum. The red cell sedimentation was normal.

**Case 7.** At the age of 4 ½ years this girl got measles and 2 weeks later erythema nodosum, with a positive Pirquet test; over both lungs bronchitic sounds could be heard. The radiograph of the lungs showed a hazy left top, while at the left side, above and next to the heart, hazy shadows were present, partly with sharp confines. The right hilum was somewhat broadened and in the right middle zone small hazy shadows were visible. The urine was normal. From the stomach lavage no tubercle bacilli could be cultivated.

Three months after the measles she was admitted to the Sanatorium (in Febr. 1934). Dullness on percussion over the left lung top in front and behind; on auscultation weakened breath sounds over these zones. The radiograph of the lungs showed a hazy infiltration in the left upper zone and further bilaterally many irregular miliary spots. The general condition was fairly good. Now from the stomach lavage tubercle bacilli could be cultivated. On the radiograph of the lungs the deviations gradually decreased with calcification of the infiltration in the left upper zone. Some months after admission no tubercle bacilli could be cultivated from the fasting stomach content. The temperature for a long time remained irregular and subfebrile. The red cell sedimentation also during many months remained increased. As particularities during the further nursing could be observed a lichen scrofulosorum, conjunctivitis phlyctenulosa and recurrent bronchitis.

During two years the girl stayed in the Sanatorium. Two years after discharge the objective impression was an excellent one. The infiltration in the left upper part was calcified, the miliary spots no longer were visible. One year later her condition had remained excellent.

**Case 8.** This girl, whose father had died of tuberculosis, developed when 5 years old a hilar process at the right side with compression cough. One month later a general dissemination over both lungs was present and still one month later the radiograph of the lungs showed a coarse miliary to cloudy picture. After another month there was a collapse of the lung in the right lower zone, which had disappeared some months later. The Pirquet test was positive. At percussion and auscultation few deviations; the general condition was satisfactory. The temperature had slight daily variations. From the stomach content tubercle bacilli could be cultivated.

At admission to the Sanatorium, in June 1936, the girl, now 6 years old, was very pale; her feeding condition was satisfactory. At percussion and auscultation there were few particularities. The radiograph of the lungs showed a marked broadening of the middle shadow, and on both sides perihilar fine spots situated very close together. The stomach lavage repeatedly was positive. The radiographical deviations remained about the same during many months. However, the general condition deteriorated during the course of the nursing time (8 months). After some time the abdomen became swollen with abnormal resistance, especially on the right side, so that the whole picture was highly suggestive of an adhesive peritonitis. The red cell sedimentation increased. — Some months after discharge the girl died at the age of nearly 7 years; the deterioration had been a rapid one, and some weeks before death there had appeared abdominal exudate with edema of the abdominal wall, legs and face. No deviations of the urine. No necropsy. — So in this case death had occurred about two years after the first finding of a miliary dissemination on the radiograph of the lungs.

We have inserted this case to the series of chronic healed miliary tuberculosis, because here the death probably is a consequence of the complication with tuberculous peritonitis and not of the chronic miliary tuberculosis of the lungs.

**Case 9.** This boy, when 9  $\frac{1}{2}$  years old, got fever after he had been coughing for about two years; he appeared to suffer from a pleural effusion at the right side, with a positive Pirquet test. The radiograph revealed a thickening of the right hilum and many small hazy shadows in both lungs. Three months later he got a spina ventosa of the right small toe with a fistula. Some months later, at the end of May 1934, he was admitted to the Sanatorium where the radiograph of the lungs showed in the upper and middle zones numerous fine spots, somewhat larger and more irregular than usually is seen in cases of miliary tuberculosis. Further there was a hilar infiltration at the right side. Radiographs of later dates showed that the number of spots gradually was decreasing, so that finally they had disappeared altogether. A source of infection was unknown, and from the fasting stomach content tubercle bacilli never could be cultivated. During the stay in the Sanatorium the boy moreover got a scrofuloderma of the right thigh and spina ventosa at both hands, then a cold abscess near the

left elbow and right knee, and further a swelling of the right ankle joint without demonstrable bony foci. In the beginning the temperature had been subfebrile, and the red cell sedimentation was greatly increased.

When the boy was 15  $\frac{1}{2}$  years old, the radiograph of the lungs showed few deviations. There still were existing two spinae ventosae, of which one was scratched out. The diagnosis of the pathologist was tuberculosis, but no tubercle bacilli could be found. One of the spinae ventosae persisted as a fistula.

Shortly afterwards a sister of this patient died of miliary tuberculosis with tuberculous meningitis. The possibility cannot be excluded that both brother and sister have been infected by some unknown patient with open tuberculosis; at any rate it is highly improbable that the boy with his negative stomach lavage should have infected his sister from a nearly healed spina ventosa.

**Case 10.** This girl suffered from a pneumonia at the age of 4 years; she kept on coughing and when 9 years old she got a painful swelling of the left ankle. Then she still was coughing. The Pirquet test was positive. The family history was free from tuberculosis. The feeding condition was good. In Febr. 1936, when 9  $\frac{1}{2}$  years old, she was admitted to the Sanatorium with a severe swelling of the left ankle. Radiographically the skeleton of the left leg and foot proved to be very atrophic. The radiograph of the lungs showed general spotty dissemination in both lungs and a bulging shadow at the right side in the upper zone next to the vessels (paratracheal glandular swelling). From the stomach content tubercle bacilli of the human type could be cultivated. During many months the swelling of the ankle and the bony affection in this region were the dominant factors in the morbid picture. Already after some months the miliary lesions had disappeared on the radiograph of the lungs but the paratracheal glandular swelling at the right side remained. From the stomach content still many times tubercle bacilli could be cultivated; finally the culture test repeatedly became negative. The girl remained in the Sanatorium during 3 years; at discharge the foot was in a quiet condition and the fistulae which formerly had appeared, were closed.

On a radiograph of the lungs, made 5 months after the discharge from the Sanatorium, there was a scarce calcified stippling in both upper zones.

Two years after the discharge the girl appeared to be in good condition. She could go without a bridle and had no complains. The lungs at percussion and auscultation, and also radiographically showed no deviations.

**Case 11.** In this girl an appendectomy was performed when she was 12 years old, and from that time she remained ailing. At the age of 13 years a painful swelling of the right ankle developed; on admission to the hospital the diagnosis was made of a tuberculous lung affection and a tuberculosis of the right foot. The radiograph of the lungs showed the picture of a miliary dissemination and moreover a hilar infiltration at the right side. The Pir-

quet test was positive as well as the sputum. One year later she got a pleural effusion in the left lower zone; the miliary dissemination then was retroceding. The temperature always was normal, the red cell sedimentation always increased. Five months after the first examination the sputum no longer contained tubercle bacilli.

In Jan. 1936 this girl, then 14 years old, came to the Sanatorium for the first time. She now produced sputum from which tubercle bacilli again could be cultivated. The radiograph of the lungs still showed a dissemination of small noduli in both lungs, which noduli became coarser in downward direction. After some months the sputum became negative and remained so. The numerous foci on the radiograph of the lungs gradually decreased in number. After two years radiographically no deviations of the lungs could be found anymore.

In the mean time in the clinical picture were dominant the tuberculosis of the ankle and a renal tuberculosis which was developing in such a degree that at the age of 16 years a nephrectomy at the right side had to be performed. After that the general condition first declined, but the patient recovered. The radiograph of the lungs, 4 months after the nephrectomy, showed a somewhat marbled design over the lungtops, but further no deviations. Her general condition then was excellent.

However, at the age of 19 years, after an influenza, there again appeared symptoms of an affection of the left top of the lung, so that at present the girl is still nursed in a hospital. The sputum which in the beginning again had been positive, now (Jan. 1942) has become once more negative.

**Case 12.** When 12 years old this boy got influenza and after that remained ailing and listless; at the Dispensary an affection of the lung was diagnosed. Then at the age of 12  $\frac{1}{2}$  years he was admitted to a children's clinic, where the Pirquet test was found to be positive. The radiograph of the lungs showed a hematogenous dissemination in both lungs with densifying in the left upper lobe and along the right border of the heart; further bilaterally an enlarged hilum with perihilar infiltration at the right side. The red cell sedimentation was increased. In the beginning the temperature was rather elevated, especially at night. During the further stay in the clinic there was a period of fever with pains in the left elbow, accompanied by redness, swelling and functio laesa. The urine was normal. The appetite remained good and the weight regularly increased. There was no cough, no expectoration. The father formerly had suffered from open pulmonary tuberculosis, and one of his children had died of this disease.

In Sept. 1941 the boy, then 13 years old, was admitted to the Sanatorium. The general condition was moderate. In the neck at the left side a small hard gland was palpable. The thorax of the boy was distinctly asthenic. At percussion the thorax in the left upper zone in front and behind, and in the left lower zone was somewhat impaired; at auscultation there were harsh breath sounds, no rhonchi. The radiograph of the lungs showed numerous small spots which by means of an intensified pattern of the lungs appeared to cohere together. Through the left lower zone numer-

ous minute spots were scattered. Paratracheally at the right side there was a glandular shadow. The culture and G.-pig test with the fasting stomach content repeatedly were positive. The red cell sedimentation was normal. In the fundus oculi at the left side, temporally, an expired chorioiditis tuberculosa was found. The deviations found at percussion and auscultation soon disappeared. — During the stay in the Sanatorium the general condition improved. In March 1942 the reticular pattern on the radiograph of the lungs was much less pronounced; in the second intercostal space at the right side a somewhat greater spot still was visible. At the end of July the patient had a cold abscess in the left elbow.

In order to examine whether the deviations which repeatedly have been found in the blood of patients with Besnier-Boeck's disease (in protein spectrum and calcium content) also occur in these cases of chronic miliary tuberculosis, we determined the calcium content of the serum and the protein spectrum of this boy in Jan. 1942. The calcium content of the serum was 10.8 mg %, the fibrinogen content of the plasma 3.86 %<sub>∞</sub>, and the total protein content of the serum 7.5 % of which 63.5 % albumin and 36.5 % globulin, while the residual nitrogen content amounted to 0.25 %<sub>∞</sub>. All these values appear to be fairly normal ones (compare also case 13).

**Case 13.** When 14 years old, this girl suffered in Jan. 1941 from influenza, and some months later she got a pneumonia and a pleural effusion at the right side. On account of this she was taken into the hospital in April 1941 and while there she got a pleural effusion at the left side. On the radiograph of the lungs of the beginning of June 1941 there was visible at the right side an interlobar line and paratracheally a compact shadow compound of two parts; further diffusely in both lungs many tiny and coarser spots. The Pirquet test and the sputum were positive. The red cell sedimentation was high. The general condition greatly improved during the half a year's stay in the hospital. In Aug. 1941 the percussion sound at the left side in the lower zone was dull over a space one hand's breadth; auscultation there revealed weakened breath sounds and intensified vocal fremitus, but no rhonchi. Radiographically the shadow at the right side paratracheally was somewhat enlarged. In the left hilum also now a more compact shadow could be seen. The foci over both lungs still were present, but less pronounced. The temperature high till subfebrile in the beginning, became normal after some months. The source of infection was unknown.

In Nov. 1941, when the girl was 15 years old, she was admitted to the Sanatorium. The percussion note over the thorax at the right upper part and the left lower part behind was impaired. The left lung border was somewhat less movable than the right one. At auscultation no distinct deviations. The radiograph of the lungs revealed that the right sinus phrenico-costalis was veiled; the right hilum was infiltrated. In the left lower zone was a remnant of a pleural effusion and in the left lung was a pronounced pattern.

In the fundus of the left eye a somewhat pigmented circumscribed focus was present, which suggested a healed tubercle. The culture and G.-pig test

with the stomach content were positive (human tubercle bacilli). The sedimentation rate of the red cells was somewhat increased. Shortly after admission the girl sprained her left ankle; swelling arose and painfulness at palpation at the medial side of the right ankle joint, which after some weeks still were present and at puncture produced some drops of clear fluid. The culture test with this fluid was negative; the radiograph did not reveal a bony focus nor any atrophy. The cartilage of the joint was unchanged.

In Jan. 1941 the calcium content of the serum was normal, the total protein content 7.89 %, viz. 3.2 % globulin and 4.67 % albumin; so the value for the globulin was slightly increased.

**Case 14.** This boy, when 9 years old, suffered from pneumonia, from which he only slowly recovered; then after examination by the school-physician he was sent to a children's hospital, though there did not exist any particular complaints. The feeding condition was satisfactory. The Pirquet test was positive. The radiograph of the lungs revealed remnants of a right pleural effusion and changes in the tissue of the lung below the right hilum. Further there appeared to exist an inveterate spondylitis of the 4th and 5th lumbar vertebrae. The stomach content was some times positive, later on negative. The source of infection remained unknown.

In the beginning of Dec. 1939, at the age of 9  $\frac{1}{3}$  years, the boy was admitted to the Sanatorium; then his condition was moderate. At inspiration the excursion of the thorax at the right side was distinctly impaired. The radiograph of the vertebral column revealed an extensive destruction of the 4th and 5th lumbar vertebrae with disappearance of the intervertebral disk; the spondylitic process still was active. The radiograph of the lungs showed a great number of tiny spots; the mediastinum was somewhat broadened. The red cell sedimentation was always increased. The fundus oculi showed no particularities. The stools often had a pappy consistency and occasionally contained much fat. The provisional diagnosis was: dissemination of foci in both lungs, with pleural thickening in the right lower zone; spondylitis of the 4th and 5th lumbar vertebrae; probably also tuberculosis of the mesenterial glands. — In the beginning the temperature was high, then it decreased during the long lasting nursing time.

Now, in Aug. 1942, the boy practically has recovered, apart from tuberculous bacilluria; also the abdominal process has quietened as far as the resorption of ingested food is concerned.

*5. In how far were the criteria mentioned sub 3, present in the above-mentioned cases?*

a) Tuberculin tests. In all cases these were positive. To this we can add that all the communicated cases, apart from two exceptions — the cases 3 and 6, in which the children were younger — were concerning children who at the moment when the diagnosis of miliary tuberculosis was made were older than 3 years.



b) The existence of a contact infection. In most cases a source of infection could be indicated in the nearest environments.

c) The demonstration of tubercle bacilli in the gastric lavage or in the sputum. In 9 cases out of the 14 the culture or G.-pig test or both have been performed with the fasting stomach content. In 8 out of these 9 cases these tests were positive. Four times tubercle bacilli of the human type could be isolated.

d) The presence of lesions outside the lungs, which only could have arisen hematogenously. The following list enumerates the changes which in the various cases with more or less certainty can be reckoned to such lesions:

case 1: coxitis.

- » 2: swelling of the left thumb, without radiographically demonstrable changes of the thumb.
- » 3: scrofulodermata on the abdominal wall.
- » 4: spondylitis.
- » 5: coxitis.
- » 6: chorioiditis tuberculosa?
- » 7: lichen scrofulosorum.
- » 9: spinae ventosae, scrofuloderma; swelling of the right foot-joint; cold abscess near the left elbow and right knee.
- » 10: swelling of the left ankle, the tuberculous nature of which however could not be proved.
- » 11: swelling of the right ankle; renal tuberculosis.
- » 12: pain in the left elbow with redness and swelling; later on cold abscess of the left elbow; chorioiditis tuberculosa.
- » 13: chorioiditis tuberculosa?
- » 14: spondylitis.

e) As concerns the spreading of the foci in both lungs and the presence of *small* foci of about the same size, also this condition has been fulfilled in the greater part of the described cases. In the beginning the radiograph of the lungs showed in all cases a homogenous spreading of innumerable foci in both lungs. The shadows were either fine (cases 1, 3, 4, 6, 7, 8, 9, 11, 12, 14) or coarse (cases 2 and 10), or of varying size (cases 5 and 13).

In most cases the radiograph also revealed a hilar infiltrate and practically always besides this a highly pronounced paratracheal swelling of glands. Frequently an early calcification of many foci was found.

### 6. *Ways of explanation.*

Especially of late several authors have tried to find an explanation for the fact that miliary tuberculosis (of the lungs) not seldom takes a protracted course and that these cases frequently recover. In this way different hypotheses have been suggested on the chronic miliary dissemination. However, in asking oneself whether these different ways of explanation are supported by a sufficient number of cases and arguments, in our opinion this question must be answered in the negative. Therefore, with reference to the cases mentioned above, and to data from the literature we want to give once more a short review of these different hypotheses, in order to attain a better founded, acceptable explanation of the pathogenesis.

A. There is no question about a miliary dissemination, but one has to deal here with *multiple, exogenic infections* or with a *bronchogenous dissemination*, f. i. by perforation of a tuberculous gland. — It does not wonder that such relatively simple explanations could come in the foreground. For the innumerable miliary or coarse foci, which in chronic miliary tuberculosis are found besides other deviations on the radiograph of the lungs, in the further course frequently show changes in character and extension. In the case of chronic miliary tuberculosis with a favourable course the foci become much denser. They may disappear totally, but there occur cases in which they still become denser, and thus show changes which are quite common in foci of indisputable exogenic origin. So in his judgment one has to ascribe special significance to the deviations which especially in the beginning were visible on the radiograph of the lungs, and to the metastases existing outside the lungs. If the (fine and coarse) foci were innumerable in the beginning, then the possibility could be excluded that one has to deal with a multiple infection, the more so when next to a highly suspected radiograph of the lungs, also distinct proofs are present for the existence of a hematogenous dissemination in organs outside the lungs.

We directly have to add here that of course the possibility remains that after the expiration of a healed hematogenous (or bronchogenous) dissemination a new exogenic infection occurs. And this possibility has to be considered especially when this new infec-

tion again shows the characteristic picture of a primary complex or — in order to use the name introduced by Schwartz — of a starting complex. Schwartz himself lately gave several examples of such cases; a. o. that of a girl, aged 7 years, in which radiographically and anatomically numerous minute scars (calcified foci) had been found in the lungs, which had to be regarded as remnants of a tuberculous infection of a long time ago. In these foci no tubercle bacilli could be demonstrated. Next to this there existed a fresh primary complex in one lung with fresh hematogenous dissemination in lungs, spleen and kidneys (compare also Terplan). However, in these cases the foci rarely will be present in such a large number that the picture of miliary tuberculosis arises.

Neither can we accept for the majority of our cases the hypothesis, that the picture could be explained by a bronchogenous dissemination. Such an explanation could only be taken into consideration when the radiographically demonstrable foci should be localized principally in one lung, or in both lungbases, while other symptoms of a hematogenous dissemination as a rule are absent. — We further can add, that in chronic miliary tuberculosis pathologically the localization of the deviations in the lungs (primary in the interstitium) is different from that of the primary lesions in exogenic aerogenic infections or in a bronchogenous dissemination (primary alveolitis and endobronchitis).

B. Explanation of the chronic miliary tuberculosis by a *lymphogenous dissemination*.

Various authors have remarked that in judging a hematogenous dissemination due attention should be paid to the conduct of the lymphatic system. This first of all is due to the consideration that this dissemination rather often originates from caseated lymphglands; secondly to the fact that there occur (rare) cases of tuberculosis, which principally take the course of a tuberculosis of the lymphglands (compare a. o. Pagel); and further one has to consider the fact that a hematogenous dissemination not rarely is followed by a disease of the lymphvessels, so a spreading along the lymphways (lymphangitis reticularis of Hanseemann and of Schürmann). The clinical picture of such a lymphangitis reticularis could be that of a chronic hematogenous tuberculosis (a. o. Assmann and Hantschmann). Radiographically the lungs in these cases should show, next to a fine stippling, also a pattern of fine web-like appearance, where

in the meshes of this network are situated minute spots, thus a picture resembling that in lymphangitis carcinomatosa.

The further clinical and radiographical course in such cases of lymphogenous dissemination — as described a. o. by Schürmann — is, however, greatly differing from what we could observe in our cases. For the chronic interstitial proliferation of connective tissue, which occurs in cases of lymphangitis tuberculosa, frequently should lead to highly pronounced dyspnoea and a striking cyanosis, eventually also to emphysema. In the long run there exists the possibility that also hypertrophy of the right ventricle and decompensatio cordis may arise. And the lungs should show, next to the disseminated tubercles, typical round or nearly round roles, without any infiltration of the surroundings, and which radiographically should be characterized by round or oval clearings. — Further in studying the descriptions of cases of lymphangitis reticularis, one gets the impression — and this also holds true for part of those cases described as cases of tuberculosis of the lymphglands, namely those in which caseification was lacking — that repeatedly one had to deal with cases of Besnier-Boeck's disease (compare a. o. Pagel). However, at present the tuberculous etiology of this disease is by no means an irrefutable fact and the localisations which in this disease may occur also elsewhere in the body, so outside the lungs, usually have another aspect than those found in most cases of chronic miliary tuberculosis outside the lungs. Moreover it is difficult to understand that a lymphogenous spreading should give rise to the picture of (chronic) miliary tuberculosis, as this would mean a spreading contrary to the direction of the normal lymph stream (compare a. o. Fish).

Besides, different authors assume that in lymphangitis reticularis of tuberculous etiology there principally should exist a process localized in the lungs (compare a. o. Miller). But even in this line of thoughts the explanation of the healed miliary tuberculosis by means of lymphogenous dissemination is only acceptable at the utmost for a small part of the cases, as usually the process is not restricted to the lungs.

So though the possibility cannot be denied that the picture of chronic miliary tuberculosis may occur by means of a lymphogenous dissemination, still one must be rather sceptic in face of the data about the frequency of this lymphogenous dissemination in the cases of healed miliary tuberculosis.

In the case of Hoyle and Vaizey, where a lymphogenous spreading was accepted based on the radiographic and the necropsy features, the tuberculous etiology was by no means ascertained. In the anamnesis there was no contact with tuberculosis, the family history was also free from tuberculosis and in the sputum no tubercle bacilli could be found, though it has been examined 5 times. Also in the mucus, obtained by a bronchoscopy, these bacilli were absent. And finally also after death no tubercle bacilli could be found in six different slides of the lungs, nor in two slides of lymph-glands. — Fish was unable to find in any of the cases which came to autopsy (6 out of 10) an indication for a lymphogenous spreading in the lung.

C. Another hypothesis assumes that in the explanation of the chronic course of a miliary tuberculosis the *quantity of the disseminated tubercle bacilli* in the blood stream should be of great significance, and the *repetition* of the dissemination. This hypothesis has been suggested a. o. by Hein and by Miller. In the chronic miliary tuberculosis one should have to deal with a dissemination occurring only once or when recurring only with a relatively small quantity of bacilli. This contrary to the acute miliary tuberculosis where, according to most current conceptions, a massive rupture of a veine tubercle respectively a continuous dissemination in the blood stream takes place.

As arguments in favour of this above-mentioned hypothesis we can mention:

1. The relatively rare occurrence of meningitis in chronic miliary tuberculosis (in childhood). Of 104 cases, collected by Hoyle and Vaizey from the literature (we will not discuss here whether in reality all these were cases of chronic miliary tuberculosis according to the present criteria), only 9 patients died of meningitis, viz. the 2nd case of v. Muralt, the case of v. Kern and Johan, the 2nd case of Deul, the 18th case of Delarue, the first case of Rist c. s. (1926), the 2nd case of Schwenk and the cases resp. of Pilger, Edel and Jaquerod. This number stands in sharp contradiction to the frequency of meningitis in acute miliary tuberculosis

2. The fact that in 3 observations of our own there were indications for the existence of a tubercle in the chorioidea, while no meningitis arose.

The patient of Ladenius, described in the thesis of Duyster, had in the beginning one tubercle in the fundus, later on a second. Five years after the first examination this patient was still in good condition.

In the rare cases of chronic miliary tuberculosis, where a number of tubercles were found to be present in the chorioidea, the patient later on died indeed from meningitis (compare in this connection a. o. the case described by v. Kern and Johan).

As arguments contrary to the above-mentioned hypothesis one could advance however, that from the literature it has clearly appeared that clinically no sharp division can be made between the acute miliary tuberculosis and the chronic form with an usually favourable prognosis; different kinds of forms with greatly varying clinical course, may occur. In the forms with a chronic course not seldom a renewal of the symptoms of activity is seen (fever, red cell sedimentation, morphological blood picture) at the same time with the occurrence of new, extra-pulmonary localizations. This could be explained best by assuming a recurrence of the bacillaemia. In the cases with a chronic course which come to autopsy, indications for this conception can be found in so far as in the lungs (and often in other organs) characteristic acute miliary tubercles, fibrous nodules and eventually calcified tubercles are present at the same time.

D. Still another way of explanation finds its starting-point in the following. Different authors were struck by the fact that in cases of chronic miliary tuberculosis with a lethal and non-lethal course the radiograph of the thorax often revealed a pronounced broadening of the upper mediastinal shadow. We were able to observe this also nearly constantly in our cases. In the cases which came to autopsy, on this place often numerous large caseated paratracheal glands were found. Now these paratracheal glands in the upper part of the mediastinum should form the last line of defense against the passing of the tubercle bacilli into the blood stream — such as indeed has been demonstrated by Ghon, Kudlich and Schmiedl. The presence of these caseated glands would explain the inclination to the recurrent tuberculous bacillaemia. Now the conception is this: while in the acute miliary tuberculosis the lung cannot act sufficiently as a filter because issuing from the *veine tubercle* a massiv quantity of tubercle bacilli enters into the circulation, or because the *veine tubercle* is situated in the lungs, this filter-action is effective in chronic miliary tuberculosis. This effectiveness is based either on the fact that the point of issue of the miliary tuberculosis is situated at the venous side of the circulation, thus in one of the organs before the pulmonary circulation (a), or in the fact that

this focus is situated in the mentioned lymphglands of the mediastinum itself (b). In both cases the possibility exists that in a dissemination which occurs only once, the lung acts as a filter.

sub (a). The point of issue of the chronic miliary tuberculosis is situated at the venous side of the circulation. In our opinion there are some arguments for the supposition that this focus often is localized at the pulmonary side of the right heart; a. o. the fact that in cases with a lethal course liver, spleen and kidneys repeatedly contained only very few tubercles, and further the fact, that in cases of chronic miliary tuberculosis the miliary dissemination not rarely was preceded by a bony focus.

This occurred a. o. in one of our own cases (number 1), in the 2nd, 3rd, 5th and 10th case of Hoyle and Vaizey, in 3 cases of Hein (cases 2, 10 and 20), in the cases of Courtin and Duken, in that of Acufia and Bazán, in another case of Duken and probably in the first case of Plieninger.

The third case of Hoyle and Vaizey i. e. was that of a girl, 16 years old, who showed as first clinical lesion a tuberculosis of the left tarsus, which preceded the further manifestation by about 8 months.

sub (b). Spreading along the lymphglands of the mediastinum, ductus thoracicus, vena subclavia, etc. In favour of this possibility are those cases where a tuberculosis of the ductus thoracicus had been found (compare a. o. the case, reported upon by Burnand), and those cases in which a caseated glandular tuberculosis was present. To these last mentioned cases are belonging the 2nd case of Rist c. s., the 3rd case of Edel, and the first one of Pierson.

Very important in connection to this way of explanation (sub D) is especially the case of Trémolières and Moussoir, where at autopsy, besides caseated bronchial and mediastinal glands, also were found a. o. miliary tubercles on the valves of the right heart.

However, we may not conceal the fact that most of the cases cited here were no cases of chronic healed miliary tuberculosis, but concerned patients with a chronic miliary tuberculosis who had died. So they do not belong to the series of chronic miliary, tuberculosis in the more limited sense. But still these cases may lead to a better insight into the pathogenesis of the chronic miliary tuberculosis, and for that reason they have been cited here.

E. The chronic miliary tuberculosis is caused by a dissemination of dead or weakened tubercle bacilli. The dissemination of dead or weakened tubercle bacilli should lead to modifications in the con-

ditions of immunity and in this way also gives rise to other pathological reactions. In this connection Burton-Wood has suggested that the chronic miliary tuberculosis should be an exsudative phenomenon.

The allergic reaction should be the cause that no typical tuberculous tissue is formed but a more atypical inflammation tissue, which may be resorbed again. The conception of Nicaud that dead bacilli play an etiological rôle in the occurrence of chronic miliary tuberculosis, is excluded by the fact that during the life of patients with chronic miliary tuberculosis frequently virulent tubercle bacilli could be cultivated from sputum or stomach content, or from localizations in different organs; further by the fact that these tubercle bacilli also after an eventual death regularly could be demonstrated by staining or by the culture or G-pig test in large amounts.

It is quite well acceptable, however, that weakened tubercle bacilli play a rôle here, and practically this comes all to the same thing. Weakened tubercle bacilli indeed may originate from a primary focus, which is the cause of positive sputum. Then we have only to accept that this decreased virulence has arisen along the way from the lung via a chain of lymphglands of the mediastinum to the ductus thoracicus, and from there to the blood stream (vena subclavia), in which tract the lung also may serve as a filter.

The following arguments plead in favour of the hypothesis of weakened bacilli being the principal factor:

a. cases of chronic miliary tuberculosis, accompanied by lupus. Plieninger, Hein and Rist (1937) have communicated such cases.

The case of Rist (1937) concerned a boy aged 14 years, who had a dry cough already for 2 years. Feeding condition was very good. The radiograph of the thorax showed a fine mottled miliary tuberculosis in both lungs. No deviations at percussion and auscultation. Since one year the patient has lupus of the right elbow and of the neck. Tuberculin test highly positive. 16 Months later: no more cough; the lupus spots have remained the same. The radiograph of the lungs shows a marked clearing of both lungs. 21 Months after the first consultation: the general condition is excellent, the radiograph of the lungs is normal. 10 Months later: the patient coughs in the morning with slight expectoration. Shortened percussion and weakened breath sounds over the right upper lobe. Radiograph of the lungs: cavity in the right upper lobe; no trace of miliary dissemination. The



sputum was positive. General condition good, no fever. Already 3 months later the cavity nearly totally had disappeared and been replaced by a dense shadow. Tubercle bacilli now were absent in the sporadical sputum. Still one year later: general condition good. The radiograph of the lungs shows no trace of a former cavity. Another 2 years later: general condition excellent. The patient regularly is at work. The radiograph only reveals a partly calcified scar. The lupus spot in the neck is healed, that at the elbow still persisting. No particularities at percussion and auscultation.

b. The cases in which papulo-necrotic tuberculides appeared to exist as it is usually accepted in this affection that they are caused by tubercle bacilli of decreased virulence. The occurrence of tuberculides has repeatedly been observed in chronic miliary tuberculosis (in 12 of 120 cases, collected by Hoyle and Vaizey), o. a. by Kutznitzki and Bittorf, Hitzengerber, Marlow, further by Miller and Fish, and in nr. 7 of our own cases.

c. The cases of chronic miliary tuberculosis with a benign course in very young children, aged only some months. Such cases have been described a. o. by Zarfl (however, in this case the tuberculin test 3 times was negative) and by Duken (3 cases in babies).

The 2nd case of Duken was that of a boy aged 5 months. It was a premature infant, birth weight 2000 grams. Already during the first 3 months of life the child o. a. suffered from a severe cough and practically it did not increase in weight. The mother had died from tuberculosis when the child was 3 months old. The tuberculin test was already positive when the baby was aged 2 months. Examination when the boy was 5 months old: occasional fever; the child is skinny, slightly cyanotic and shows severe rickets. No deviations in the lungs at percussion and auscultation. Liver and spleen are greatly enlarged. The radiograph of the lungs showed the typical coarse mottling of miliary tuberculosis. Many tubercles of the skin, occurring with intermissions. In the further course gradual improvement was observed. The radiograph of the lungs at the age of 1  $\frac{3}{4}$  years showed complete clearance.

F. Explanation of the chronic miliary tuberculosis by *co-operation of several factors*.

Thus the five above-mentioned ways of explanation have passed in review and have been discussed. We are of opinion that the first one (multiple exogenic infections or bronchogenous dissemination) had to be rejected. The second one (lymphogenous dissemination) in our opinion, only can be applied to a limited number of cases. Each of the three other hypotheses (dissemination

occurring once, or if recurring, with a small quantity of tubercle bacilli; bacilli of decreased virulence, respectively an allergic reaction which causes atypical inflammation tissue, which may be reabsorbed; the explanation by the filter-activity of the lung along the venous way or along the lymph glands can explain only part of the particularities of the morbid picture. But each of them leaves unaccountable the other clinical particularities which could be observed in our own cases and in that of others. So we had to consider in how far the occurrence of the chronic miliary tuberculosis has to be ascribed to the co-operation of several factors. We are of opinion that indeed many facts are speaking in favour of this conception and especially we are thinking of the possibility that the cause lies in a limited dissemination of tubercle bacilli with decreased virulence, which reach the vena subclavia via the lymph glands of the mediastinum and the ductus thoracicus, and in this way pass into the blood stream. Thus this way of explaining the chronic miliary tuberculosis encloses the hypotheses mentioned sub C, D and E, and makes clear many clinical particularities of the morbid picture which have been discussed here. Especially in this way it becomes comprehensible why the prognosis of the hematogenous dissemination in this chronic miliary tuberculosis as a rule contrasts so favourably with that of the acute miliary tuberculosis, where according to the current explanation one factor is determining the prognosis, viz. the perforation of the veine tubercle.

### Summary.

This article in the first place deals with the differential diagnosis of the chronic miliary tuberculosis of the lungs against non-tuberculous affections in which the radiograph of the lungs shows multiple minute spots. Then the criteria are enumerated which as much as possible should be fulfilled for the making of the diagnosis of chronic miliary tuberculosis. This is followed by a report on 14 cases of chronic miliary tuberculosis in children, which in the course of years could be observed in the Children's Sanatorium »Hoog-Blaricum» (Holland), and which, with one exception, all had a quoad vitam favourable course. All cases are tested with reference to the above mentioned criteria. Then follows a detailed discus-

sion of the different explanations of the pathogenesis of chronic miliary tuberculosis. The opinion is pronounced that the cause of this morbid picture should be ascribed to the co-operation of different factors which make the arise of the disease comprehensible, and which moreover makes evident why the prognosis of chronic miliary tuberculosis as a rule contrasts so favourably to that of acute miliary tuberculosis.

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(From the Department of Pharmacology, University of Copenhagen,  
Chief: Professor Knud Møller M.D.)

## Hunger and Pains brought on by Ingestion of Adrenaline.

By

GEORG C. BRUN.

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As will appear from a previous publication (1942), it has been demonstrated that peroral administration of 2—3 mg adrenaline dissolved in 4—6 cm<sup>3</sup> 35 vol. % alcohol to patients suffering from gastric ulcer in nearly all cases, though sometimes only after repeated ingestion, gave rise to dyspeptic symptoms in the form of oppression and pain, sometimes nausea, which closely resembled the spontaneous symptoms of the patients. In some cases the attacks subsided spontaneously in the course of 10—15 minutes. In other instances, in which the symptoms persisted, the pain generally soon disappeared after ingestion of nitroglycerin.

Simultaneous registration of the contractions of the stomach by the balloon method showed that vigorous hunger contractions developed a pressure of 15—25 mm Hg, lasting for 3—10 seconds, which was bound to cause a closing of capillaries and veins.

Continued experiments with ingestion of adrenaline in alcohol on a further nine patients suffering from gastric ulcer fully confirmed the previous observations.

How exactly the spontaneous ulcer symptoms of the patients could be reproduced by means of adrenaline, even when they tended to take the form of the so-called pylorospastic attacks, is best shown by the following example.

A man, aged 50, had been admitted to the Rigshospital with the diagnosis duodenal ulcer. For the last 20 years he had suffered from dyspepsia, the symptoms being repeated vomiting 5—6 hours after meals, preceded by some oppression 10—15 minutes before the vomiting. The attacks occurred in the spring and autumn. They came on and subsided quite abruptly. While in hospital the patient was free from symptoms.

This patient was given 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol.<sup>1</sup> Nine minutes later he complained of discomfort, distension, faintness and perspiration. Shortly after there was oppression across the epigastrium with strong nausea and water in the mouth; the patient was on the point of vomiting. After this the symptoms subsided in the course of 5—6 minutes. According to the patient's statement the whole attack closely resembled his spontaneous dyspeptic symptoms.

The question as to the similarity between the spontaneous dyspeptic symptoms and those produced by adrenaline is of considerable interest. Does adrenaline merely lead to stimulation of the pain-perceptive nerves of the stomach, or does it produce an actual morbid condition?

The symptoms of the ulcer patients after ingestion of adrenaline bore a striking resemblance to a recurrence of their illness, and the circumstance that many hours after the dyspeptic symptoms caused by the ingestion of adrenaline had subsided, some patients suffered renewed pains and oppression pointed in the same direction. But it is of course impossible to decide whether these spontaneous attacks would not have come on even if the patients had not been given adrenaline.

The following experiment on a woman, aged 27, who had never previously had dyspepsia, definitely seem to indicate that a single ingestion of adrenaline is able to produce a slight morbid condition.

Few minutes after ingestion of 3 mg adrenaline in 35 % alcohol a sensation of suction and oppression came on which rapidly became fairly pronounced and caused discomfort. Gradually nausea set in too, and one moment the subject was on the point of vomiting. After well over half an hour the symptoms had subsided, but in the evening, 5—6 hours later, there was a recurrence of nausea and oppression which persisted for many hours. For the next two days the subject felt well, but both evenings, there was oppression and nausea which did not subside until she lay down to sleep.

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<sup>1</sup> As in all the other experiments in this work, the solution used was the solutio adrenalini hydrochloridi of the Pharmacopoea Danica, diluted with aliquot parts 70 % alcohol.

## The Effect of Adrenaline Ingestion on Patients suffering from Achylia.

The idea is probably still very generally entertained that the pains of ulcer patients are caused by the gastric juice irritating the ulcer or the inflamed mucosa.

Oline Christensen's (1931) demonstration of the close connection between the contractions of the stomach and typical hunger pains, and the independence of gastric acidity of the ulcer pains, shows very clearly, however, that the pains may arise in other ways.

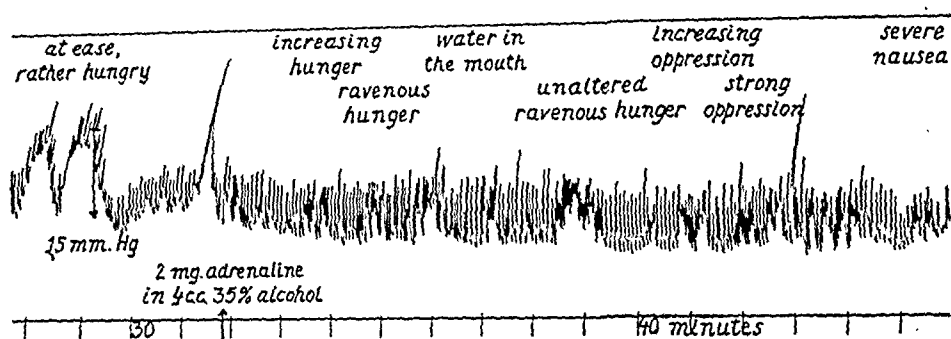


Fig. 1. Part of the gastrographic curve from the sixth achylia patient. It should be noted that the strong sensations of hunger and oppression were felt while the stomach was practically quiescent.

In order to find out whether there was after all reason to suppose that the adrenaline was not the primary cause of the pain in the ulcer patients, but that the pains only came on if acid was simultaneously present in the stomach, I have tried the effect of peroral administration of adrenaline to patients suffering from achylia. Six patients suffering from achylia refractory to histamine were given the usual doses of adrenaline in alcohol.

Four of the patients were subject to frequent dyspeptic symptoms, manifesting themselves in three of them as oppression immediately after meals. In the fourth patient, who also suffered from diabetes, the pains came on without any relation to meals. The only dyspeptic symptoms of the fifth patient were, in the main, heartburn and eructations. All five patients felt perfectly well at the beginning of the experiment. 3—8 minutes after ingestion of only 2 mg adrenaline in 4 cm<sup>3</sup> 35% alcohol they all showed dyspeptic symptoms in the form of oppression and moderate to very severe pain in the epigastrium, as well as nausea. Two of the patients vomited. The symptoms recalled the spontaneous symptoms of these patients both as to their nature and localisation.

A sixth achylia patient, a man aged 55, who suffered from fibrous tuberculosis of the lungs and from a refractory simple anaemia with a haemoglobin percentage of 60, had never known pain or oppression in the upper region of the abdomen. He would eat and tolerate all kinds of food. This patient felt a very strong sensation of hunger a few minutes after the ingestion of 2 mg adrenaline. He did not remember ever having felt such intense and burning hunger before; at the same time the stomach was quiescent without any hunger contractions. (Fig. 1) After 5 minutes there was incipient oppression, increasing rapidly to intense unpleasant oppression radiating from the umbilicus to the epigastrium. The patient did not remember ever having had similar symptoms before. A few minutes later he was on the point of vomiting. After this the nausea and oppression soon subsided.

The experiments showed that achylia patients were at least just as responsive to adrenaline ingestion as ulcer patients. The symptoms set in shortly after ingestion of a single small dose of adrenaline.

Thus a vasoconstrictive agent may produce typical dyspeptic symptoms in the form of oppression and pain in the epigastrium as well as nausea and sometimes vomiting in ulcer patients as well as achylia patients. *This speaks in favour of the supposition that the gastric symptoms after ingestion of adrenaline are primarily vascular phenomena, and that the adequate stimulus for the pain-percipient nerve ends of the stomach is not the action of acid but changes in the condition of vascular contraction.*

If the notion that the gastric juice may play a part in the onset of spontaneous ulcer pains is to be adhered to, and this cannot of course be excluded, we can hardly get round the presumption that the vessels must be the medium through which the gastric juice acts.

### **The Effect on Healthy Individuals of the Ingestion of Adrenaline.**

In his experiments on the effect of adrenaline A. Brems (1926) mentions that 4 mg adrenaline administered perorally to individuals who had not previously suffered from dyspeptic symptoms would now and then give rise to a sensation of suction, cardialgia, and nausea.

After the observation of the strong effect of adrenaline on ulcer patients and achylia patients a closer investigation of its effect on healthy individuals would seem to be of interest.



I have therefore carried out a number of experiments on healthy young men and women, all of them medical students, who had not previously suffered from dyspeptic symptoms of any importance.

The subjects came fasting to the experiment which took place in the morning at 8—9 o'clock. They were not told beforehand what they were given nor what its usual effect was.

In all previous experiments with ingestion of adrenaline the contractions of the stomach were simultaneously registered by the balloon method. In these experiments pronounced dyspeptic symptoms appeared after ingestion of adrenaline, both in the periods with hunger contractions and while the stomach was quiescent; the registering of the movements of the stomach during the adrenaline experiments was therefore considered of minor importance, though in some cases, for instance when the dyspepsia was felt very strongly simultaneously with the hunger contractions, such registering might indeed afford objective confirmation of the statements of the subject. — On the other hand, more natural conditions were obtained when the subject was not inconvenienced by the stomach tube.

In order to find out whether anaesthetizing of the gastric mucosa had any influence on the effect of the adrenaline, a large dose of a local anaesthetic, nupercaine (percainum »Ciba«) or benzocaine, was administered in some cases, together with a little water, as far as possible when the gastric symptoms had reached their climax. Or nupercaine was given with the adrenaline, the adrenaline solution ingested containing 1 % nupercaine hydrochloride, which is the usual dose when nupercaine is used as an anaesthetic for the mucosa.

### Experiment 1.

#### *Ingestion of Adrenaline in an Alcoholic Solution.*

Male, T. W. M., aged 23.

Periodical moderate hunger at the beginning of the experiment.

At 0<sup>1</sup> o'clock ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol.

In the course of the next 7 minutes increasing, sucking hunger, considerably stronger than at the beginning of the experiment. Thereafter moderate hunger as at the beginning of the experiment.

<sup>1</sup> The time indications refer to the number of minutes elapsed after the beginning of the experiment.

At 15' again administration of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. Some minutes later strong hunger and a sensation of suction causing some discomfort for a short time.

*The experiment showed that there was a marked increase in the sensation of hunger a short time after ingestion of adrenaline-alcohol.*

### Experiment 2.

#### *Ingestion of Adrenaline in an Alcoholic Solution.*

Female, H. L. H.—L., aged 26.

No sensation of hunger at the beginning of the experiment.

At 0 o'cl. ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. After 5' incipient hunger increasing at 10' to moderate hunger. The sensation subsided again at 21'. Slight nausea accompanied the sensation of hunger, a symptom which the subject occasionally experienced in connection with strong hunger.

At 22' again ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. After 33' again moderate hunger which almost entirely subsided in the course of 7 minutes.

*The experiment showed that a moderate sensation of hunger came on after ingestion of adrenaline-alcohol.*

### Experiment 3.

#### *Ingestion of Adrenaline in an Alcoholic Solution and of Nupercaine.*

Male, K. L. N., aged 28.

Moderate hunger at the beginning of the experiment.

At 0 o'cl. ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol.

After a couple of minutes increasing hunger with slight sensation of suction in the cardia. The marked increase in the sensation of hunger persisted for about 10 minutes. — Thereafter moderate hunger which practically disappeared after the administration at 21' of 5 cg nupercaine with 25 cm<sup>3</sup> of water.

At 25' again ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. At 30' a sensation of emptiness in the stomach and moderate hunger. During the next c. 20 minutes constant hunger at times very strong, and gradually a marked sensation of suction and tenderness under the left curvature.

*The experiment showed that increased hunger came on after the first ingestion of adrenaline. It subsided almost momentarily after the administration of nupercaine but rapidly came on again, this time accompanied by marked suction and tenderness, after a second ingestion of adrenaline-alcohol.*

Experiment 4.

*Ingestion of Adrenaline in an Alcoholic Solution and of Nupercaine and Benzocaine.*

Male, J. J., aged 24.

The subject was not usually very hungry in the morning.

No sensation of hunger at the beginning of the experiment.

At 0 o'clock ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. 2 minutes later a strong sensation of hunger and slight suction and oppression in the left side of the epigastrium. At 4' the sensation of hunger was stronger than the subject ever remembered to have felt it before. From 11' to 18' hardly any hunger, after this again increasing hunger intensified to strong hunger at 32'. At this point 5 cg nupercaine was administered with 20 cm<sup>3</sup> of water. During the next 6 minutes the sensation of hunger entirely disappeared.

At 41' again ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> of alcohol. After 45' fairly strong hunger, periodical rather unpleasant oppression, and occasionally stabbing pains in the epigastrium.

At 69' the subject drank 20 cm<sup>3</sup> of water. Directly after this the sensation of hunger subsided. A few minutes later, however, there was again strong hunger, suction and oppression.

At 77' the subject was given 10 cm<sup>3</sup> of water to drink, whereafter the sensation of hunger decreased considerably at once. After a couple of minutes, however, it recurred and was very marked at 86'.

At 87' administration of 50 cg benzocaine and 20 cm<sup>3</sup> of water. During the following minutes the sensation of hunger subsided somewhat, without, however, disappearing at any time, and at 99' fairly strong hunger was felt again.

*The experiment showed that an intense sensation of hunger came on a few minutes after the ingestion of adrenaline-alcohol. After repeated ingestion of adrenaline-alcohol suction, oppression, and stabbing pains in the epigastrium set in. Ingestion of nupercaine and benzocaine with water, and ingestion of water alone, only relieved or reduced the sensation of hunger for a short time.*

Experiment 5.

*Ingestion of Adrenaline and of Adrenaline and Nupercaine in an Alcoholic Solution.*

Male, E. E. J., aged 25.

Slight hunger at the beginning of the experiment.

At 0 o'clock ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. — From 2' to 8' steadily increasing hunger accompanied by some suction and oppression. After this the sensation of hunger gradually abated.

At 26' administration of 3 mg adrenaline and 5 cg nupercaine in 6 cm<sup>3</sup> 35 % alcohol. After 33' increasing hunger and oppression in the epigast-

rium. At 38' the sensation of hunger was as strong as anything the subject had ever felt before. There was also slight nausea. Thereafter the sensation of hunger gradually decreased.

*The experiment showed a strong increase in the sensation of hunger after ingestion of adrenaline-alcohol as well as after adrenaline-nupercaine-alcohol.*

#### Experiment 6.

##### *Ingestion of Adrenaline and Nupercaine in an Alcoholic Solution.*

Male, R. W., aged 25.

The subject was not usually hungry in the morning.

No hunger at the beginning of the experiment.

At 0 o'cl. ingestion of 3 mg adrenaline and 6 cg nupercaine in 6 cm<sup>3</sup> 35 % alcohol. At 4' there was a strong sensation of hunger, undoubtedly stronger than the subject had ever felt before. No other discomforts. 5 minutes later the hunger subsided. From 5' to 12' there was some suction in the epigastrium; after this no discomforts.

*The experiment showed that intense hunger of short duration followed by some suction in the epigastrium set in a few minutes after ingestion of adrenaline-nupercaine-alcohol.*

#### Experiment 7.

##### *Ingestion of Adrenaline and Nupercaine in an Alcoholic Solution.*

Male, E. D., aged 30.

The subject was usually hungry in the morning.

There was rather pronounced hunger at the beginning of the experiment.

At 0 o'cl. ingestion of 3 mg adrenaline and 6 cg nupercaine in 6 cm<sup>3</sup> 35 % alcohol. In the course of  $\frac{1}{2}$  minute the sensation of hunger subsided. From 3' to 10' there was first tightness and burning in the upper part of the epigastrium, then successive spells of rather severe pain in the same place.

At 16' the sensation of hunger came on again. It rapidly increased in intensity and at 27' it was stronger than the subject remembered ever having experienced it before. During the next 5—10 minutes the sensation of hunger decreased again.

At 38' ingestion of 1  $\frac{1}{2}$  mg adrenaline and 3 cg nupercaine in 3 cm<sup>3</sup> 35 % alcohol. Slight oppression was at once felt in the epigastrium and the sensation of hunger increased slightly. From 41' to 53' there were successive spells of moderate pain downwards in the epigastrium. Thereafter wellbeing and moderate hunger.

*The experiment showed that first pain and then intense hunger set in after ingestion of adrenaline-nupercaine-alcohol. After repeated ingestion moderate transient pain.*

### Experiment 8.

#### *Ingestion of Adrenaline in an Alcoholic Solution.*

Male, H. T., aged 24.

The subject was not usually hungry in the morning.

No sensation of hunger at the beginning of the experiment.

At 0 o'clock ingestion of 3 mg adrenaline in 20 cm<sup>3</sup> 14 % alcohol. No change in the condition. At 17' ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. 3 minutes later some distension which disappeared in the course of a few minutes.

At 36' again ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. After 38' slight nausea persisting for the next 17 minutes and increasing to an inclination to vomit. Also some distension.

*The experiment showed that mild dyspeptic symptoms in the form of nausea and distension came on after repeated ingestion of adrenaline-alcohol.*

### Experiment 9.

#### *Ingestion of Adrenaline in an Alcoholic Solution.*

Male, E. L., aged 24.

The subject was usually hungry in the morning.

Moderate hunger at the beginning of the experiment.

At 0 o'clock ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. — After 4 minutes rather marked oppression in the epigastrium which persisted for about 7 minutes. At the same time the sensation of hunger almost entirely disappeared.

*The experiment showed that shortly after ingestion of adrenaline-alcohol oppression in the epigastrium came on.*

### Experiment 10.

#### *Ingestion of Adrenaline in an Alcoholic Solution.*

Male, M. S., aged 25.

The subject was not usually hungry in the morning.

No hunger at the beginning of the experiment.

At 0 o'clock ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. — At about 7' slight nausea and oppression, which disappeared abruptly at 9'.

At 19' ingestion of 2 mg adrenaline in 4 cm<sup>3</sup> 35 % alcoholic solution. Immediately after the intake, nausea which persisted for 5 minutes. At 27' some hunger. The subject lighted a cigarette. After 6 inhalations of tobacco smoke all sensation of hunger had disappeared. Some minutes later, strong giddiness lasting for 3 minutes. If smoking on an empty stomach, the subject would occasionally feel somewhat giddy but never in so high a degree as in this experiment.

*The experiment showed* that after ingestion of adrenaline-alcohol some nausea and oppression came on. A moderate sensation of hunger was quickly relieved by the smoking of a cigarette. The tolerance of tobacco seemed somewhat reduced.

#### Experiment 11.

*Ingestion of Adrenaline in an Alcoholic Solution and of Nupercaine.*

Male, G. I.—L., aged 26.

The subject never felt hungry in the morning.

No hunger at the beginning of the experiment.

At 0 o'cl. ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. From 5' to 8' there was some oppression at the upper part of the epigastrium. Thereafter ease. No hunger.

At 20' ingestion of 5 cg nupercaine with 25 cm<sup>3</sup> of water; at 25' again ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> alcohol. From 41' to 45' there was again oppression in the epigastrium of the same intensity as after the first ingestion of adrenaline. No hunger.

*The experiment showed* that transient oppression in the epigastrium came on shortly after ingestion of adrenaline. Ingestion of nupercaine did not prevent oppression.

#### Experiment 12.

*Ingestion of Adrenaline in an Alcoholic Solution and of Benzocaine.*

Male, T. Ø., aged 25.

Moderate hunger at the beginning of the experiment.

At 0 o'cl. administration of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. From 4' to 13' periodical rather unpleasant oppression in the epigastrium entirely overshadowing the sensation of hunger. From 28' again increasing oppression, at times very unpleasant.

At 37' ingestion of 50 cg benzocaine and 20 cm<sup>3</sup> of water. 4 minutes later the oppression entirely disappeared. But from 48' there was again strong oppression intensified to pain persisting till 60'.

*The experiment showed* that periods of strong oppression in the epigastrium occurred up to 1 hour after ingestion of adrenaline. 50 cg benzocaine only caused the dyspepsia to subside for some few minutes.

#### Experiment 13.

*Ingestion of Adrenaline and Nupercaine in an Alcoholic Solution.*

Male, E. L., aged 25.

Pronounced hunger at the beginning of the experiment.

At 0 o'cl. ingestion of 3 mg adrenaline and 6 cg nupercaine in 6 cm<sup>3</sup> 35 % alcohol. For the first few minutes there was an appreciable decrease in the

sensation of hunger. From 6' increasing oppression across the epigastrium with slight nausea. After a short pause again about 13' increasing oppression intensified from 19' and in the next 17 minutes to rather severe pains downwards in the epigastrium. Simultaneously increasing nausea. The subject gradually grew very pale and was clearly in great distress. At 36' ingestion of  $\frac{1}{2}$  mg nitroglycerin and 6 cm<sup>3</sup> of water. 2 minutes later abrupt but only quite brief relief from oppression and pain.

In the course of the next 20 minutes twice administration of  $\frac{1}{4}$  mg nitroglycerin and 10 cm<sup>3</sup> of water. Thereafter all unpleasant sensations subsided.

*The experiment showed* that severe dyspeptic symptoms of comparatively long duration came on after a single ingestion of adrenaline-nupercaine-alcohol. Rapidly passing relief after ingestion of nitroglycerin.

#### Experiment 14.

*Ingestion of Adrenaline and Nupercaine in an Alcoholic Solution and of Alcohol alone.*

Male, J. G., aged 25.

The subject was not usually very hungry in the morning.

At the beginning of the experiment there was slight hunger.

At 0 o'clock ingestion of 3 mg adrenaline and 6 cg nupercaine in 6 cm<sup>3</sup> 35 % alcohol. For the first few minutes after this there was increasing hunger and nausea. At 7' all sensations of hunger had disappeared and the nausea had abated. There was now persistent oppression in the epigastrium, for the next 2—3 minutes intensified to very unpleasant pains in the same place. The subject turned very pale. After 20' the pains rapidly subsided, and at 26' the subject was quite restored.

At 34' ingestion of 6 cm<sup>3</sup> 35 % alcohol without ensuing dyspepsia.

*The experiment showed* that severe pains in the epigastrium came on shortly after ingestion of adrenaline-nupercaine-alcohol. No dyspepsia after succeeding ingestion of alcohol alone.

#### Experiment 15.

*Ingestion of Adrenaline and Nupercaine in an Alcoholic Solution.*

Male, V. S., aged 26.

The subject was not usually hungry in the morning.

No hunger at the beginning of the experiment.

At 0 o'clock ingestion of 3 mg adrenaline and 6 cg nupercaine in 6 cm<sup>3</sup> 35 % alcohol. At 6' slight discomfort in the upper part of the epigastrium passing into a sensation of suction in the following minutes. At about 18' minutes slight hunger. After 29' the subject was quite restored.

*The experiment showed* that mild dyspeptic symptoms came on after a single ingestion of adrenaline-nupercaine-alcohol.

## Experiment 16.

*Ingestion of Adrenaline and Nupercaine as well as Adrenaline alone in an Alcoholic Solution. Ingestion of a Watery Kephirine Solution.*

Male, O. H., aged 25.

The subject was not usually hungry in the morning.

No hunger at the beginning of the experiment.

At 0 o'clock ingestion of 3 mg adrenaline and 6 cg nupercaine in 6 cm<sup>3</sup> 35 % alcohol. From 4' to 9' marked oppression in the epigastrium of varying intensity; thereafter wellbeing; no sensation of hunger.

At 21' ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol. At about 30' there was pronounced oppression in the epigastrium of a few minutes' duration; after this wellbeing.

At 36' administration of 5 cg kephrine in 25 cm<sup>3</sup> of water. From 39' to 44' there was oppression in the epigastrium, periodically more intense than before, after which the subject again felt perfectly well.

In the period 2—5 hours after the experiment the subject vomited three times, each time about half an hour after the intake of food. There was no preceding pain or nausea, but some perspiration and secretion of saliva about 5 minutes before the vomiting.

*The experiment showed that pronounced oppression in the epigastrium of short duration came on 4—7 minutes after ingestion of adrenaline-nupercaine-alcohol, adrenaline-alcohol, and kephrine solution.*

## Experiment 17.

*Ingestion of Adrenaline and Nupercaine in an Alcoholic Solution.*

Male, H. S., aged 25.

The subject was as a rule only very little hungry in the morning.

Slight hunger at the beginning of the experiment.

At 0 o'clock ingestion of 3 mg adrenaline and 6 cg nupercaine in 6 cm<sup>3</sup> 35 % alcohol. From 5' to 11' there was moderate burning in the cardia. After this no discomfort. No hunger.

At 27' ingestion of 2 mg adrenaline and 4 cg nupercaine in 4 cm<sup>3</sup> 35 % alcohol without ensuing dyspeptic symptoms.

From 42' to 57' the subject smoked a cigarette, inhaling the smoke as he generally did. Shortly after there was some trembling of the legs. At 58' the subject swallowed some mouthfuls of tea and eat a mouthful of ryebread. A strong feeling of discomfort in the cardia immediately came on, accompanied by severe nausea. Afraid that he would vomit he rose from the table but felt so giddy and powerless that he was obliged to lie down on the floor. The subject was extremely pale and a cold sweat broke out. For the next 20 minutes there were very severe pains in the cardia in successive spells, and nausea. During this period the subject was given 4—5 nitrogly-



cerin tablets of  $\frac{1}{4}$  mg each with some relief from the pains. At 95' administration of 1 cg prisco. A couple of minutes later all discomfort had disappeared.

At 120' the subject drank half a cup of tea without any unpleasant effects of any kind.

The experiment showed that a mild dyspepsia of short duration set in after adrenaline-nupercaine-alcohol. Immediately after the smoking of a cigarette with the intake of food severe pain, nausea and mild collapse came on. Administration of vasodilating remedies had no great effect.

#### Experiment 18.

##### *Ingestion of Adrenaline and Nupercaine in an Alcoholic Solution.*

Male, E. H., aged 25.

The subject was as a rule somewhat hungry in the morning.

At the beginning of the experiment there was moderate hunger.

At 0 o'clock administration of 3 mg adrenaline and 6 cg nupercaine in 6 cm<sup>3</sup> alcohol. From 3' to 18' oppression in the epigastrium of varying intensity, thereafter comfort. Merely a slight sensation of hunger.

At 30' ingestion of 2 mg adrenaline and 4 cg nupercaine in 4 cm<sup>3</sup> 35 % alcohol. From 31' to 49' some oppression in the epigastrium; after this no discomfort. At 42' the subject smoked a cigarette, inhaling the smoke without any resulting discomforts.

The experiment showed that oppression in the epigastrium of about a quarter of an hour's duration set in after twice repeated ingestion of adrenaline-nupercaine-alcohol. No discomforts after succeeding cigarette smoking.

#### Experiment 19.

##### *Ingestion of Adrenaline and Nupercaine in an Alcoholic Solution.*

Male, J. R., aged 25.

The subject was generally somewhat hungry in the morning.

Moderate hunger at the beginning of the experiment

At 0 o'clock ingestion of 3 mg adrenaline and 6 cg nupercaine in 6 cm<sup>3</sup> 35 % alcohol. After 12' no hunger. At 22' again incipient hunger. No dyspeptic symptoms.

The experiment showed that no sure reaction set in after ingestion of adrenaline-nupercaine-alcohol.

## Experiment 20.

*Ingestion of Adrenaline in an Alcoholic Solution.*

Female, G. H.—J., aged 24.

No sensation of hunger at the beginning of the experiment.

At 0 o'cl., 24', and 47' ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol.

The condition of the subject remained quite unchanged. Neither hunger nor dyspeptic symptoms occurred.

*The experiment showed* that no reaction whatever set in despite a three times repeated ingestion of adrenaline-alcohol.

*Experimental Results.*

The experiments showed that in most cases healthy individuals developed pronounced symptoms after a single or two to three times repeated ingestion of a few mg adrenaline in an alcoholic solution. Only in 2 individuals out of 20 no effect was observed.

The symptoms were hunger and discomfort, increasing to pain and nausea.

Since the subjects were all fasting and several of them already more or less hungry at the beginning of the experiment, special criteria were needed to warrant the conclusion that the hunger had been produced by the ingested adrenaline. Such proofs were found partly in the circumstance that in some cases (experiments 4, 5, 6, and 7) the sensation of hunger was more intense than the subjects remembered ever having felt before, partly in the fact that the sensation of hunger as a rule came on from 2 to 10 minutes after the ingestion of adrenaline, and after having subsided recurred in several instances after repeated ingestion of adrenaline (Experiments 1, 2, 3, 4, and 5).

Hunger occurred alone only as a rare exception. It was nearly always accompanied by other symptoms, principally by suction in the epigastrium. The subjects stated that there was an essential difference between the sensation of hunger and the sensation of suction.

The sensation of discomfort in the epigastrium varied in nature but were not different from those of which patients suffering from dyspepsia complain. Thus there was distension, tightness, and burning; a sucking sensation of emptiness, oppression and pain. The dyspeptic symptoms were localised to the upper, left, right, and

lower part of the epigastrium. In some few cases there was pain around the umbilicus.

Neither hunger nor dyspepsia seemed to be affected by the local anaesthetics ingested. It is true that in some instances (Experiments 4 and 12) an intense sensation of hunger or oppression was observed to subside wholly or partly after ingestion of nupercaine or benzocaine, but the hunger was also seen to disappear after the intake of 10 to 20 cm<sup>3</sup> of water (Experiment 4). And moreover, hunger and dyspepsia often quickly recurred, at any rate before there was reason to believe that the effects of nupercaine or benzocaine had as yet subsided.

In other instances (Experiments 5, 6, 7, 13, 14, 15, and 18) hunger and dyspepsia occurred shortly after simultaneous ingestion of adrenaline and nupercaine. The symptoms here seemed to set in quite apart from the fact that a local anaesthetic had been administered.

The duration of the effect of the nupercaine could be judged from the feeling of anaesthesia experienced by the subjects on the tongue and in the pharynx after they had drunk the adrenaline-nupercaine solution; it was as a rule still distinct after 30—40 minutes.

Another fairly common symptom was nausea of varying intensity. Only in one case was there vomiting, (Experiment 16), and only a couple of hours after the experiment was finished.

The local symptoms to which the ingestion of adrenaline gave rise were in a couple of the subjects accompanied by pronounced giddiness, while others felt sleepy or languid, or had a feeling of heaviness in the head. — The more or less diffused sensation of heat in the skin which not rarely occurred may perhaps be ascribed to the alcohol ingested (2—6 g in all).

In three experiments (Experiments 10, 17, and 18) the subject smoked a cigarette after adrenaline had twice been administered. The strong giddiness coming after this in two of the subjects, one of which also presented signs of a milder collapse, would seem to indicate that the gastric symptoms, consisting amongst other factors of nausea, had reduced the tolerance of tobacco. The slight resorptive effects to which the small doses of adrenaline here employed give rise (see A. Brems, 1926), cannot presumably have had anything to do with it.

### Comments.

The experiments have shown that the action of the vasoconstrictive agent adrenaline on the gastric mucosa may produce hunger as well as dyspeptic symptoms of varying nature and intensity.

The adrenaline must be supposed to penetrate more or less deeply into the mucosa and there cause the capillaries and arterioles to contract. That this supposition is correct has been ascertained by observing the gastric mucosa of several patients suffering from various affections of the stomach through a gastroscope while an alcoholic solution of adrenaline was injected through a ureter catheter fixed to the gastroscope. After  $\frac{1}{2}$ —2 minutes you could then observe a pronounced paleness of the mucosa corresponding to the places on which the adrenaline solution had acted.<sup>1</sup>

After simultaneous ingestion of adrenaline and nupercaine hunger and dyspepsia likewise set in. It must be supposed that the nupercaine will prevent any nervous impulse whatever from arising within the region into which the adrenaline-nupercaine solution penetrates, the presupposition being of course that the adrenaline does not penetrate farther into the mucosa than the nupercaine. Of this question it is not possible to know anything with certainty; but if the symptoms were only to occur in regions which the nupercaine had not yet reached, it might be expected that these would be less pronounced and that adrenaline ingested alone would produce the strongest sensations. The experiments, however, afford no evidence whatever that ingestion of adrenaline has a stronger effect than the simultaneous ingestion of adrenaline and nupercaine.

It must be taken for granted, then, that the nervous impulses conceived as hunger or pain arise in the deeper parts of the gastric wall which the adrenaline-nupercaine solution has not reached. Of possibilities of connection between the adrenaline-nupercaine-affected mucosa and the deeper parts of the gastric wall from which the nervous impulses must be assumed to arise, only that can presumably come into question which is conditioned by the blood vessels.

As the adrenaline causes a vasoconstriction in the mucosa, there must be a retroaction on the arteries that carry blood to the

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<sup>1</sup> The gastroscopic investigations have been carried out by Professor Erik Warburg to whom I am greatly indebted.

contracted capillaries and arterioles. Even though it must be supposed that the blood is carried round the anæmic area through collaterals, the circumstance that the pulse wave is sent back from the blocked area will cause the arteries to become more distended during systole than they would be if the passage were free.

In his investigations on the reactions of the vessels of the pia Fog<sup>1</sup> has ascertained by direct observation that the blocking of arterioles with air bubbles or with small corpuscular elements caused pronounced dilatation of the small arteries proximally to the blocked area.

If the a. brachialis is compressed a rise in the systolic blood pressure of 10—15 % will appear proximally to the place of constriction, as well as an increase in amplitude of 15 % (Buchthal and Warburg 1942). This must be equivalent to an increased systolic dilatation.

Reverting to the reactions of the gastric arteries, an increase in amplitude together with a dilatation might well be supposed to be the adequate stimulus to the hunger- and pain-percipient nerves of the stomach.<sup>2</sup> The mechanism of the onset of pain would then be largely reminiscent of conditions in migraine. Graham and Wolff (1938) showed that in this affection a dilatation of a. temporalis and a. occipitalis took place during the attack. At the same time the amplitude of the pulse was greatly increased and a close connection could be observed between the intensity of the headache and the increase in amplitude. Pressure on a. carotis communis would reduce the amplitude, and at the same time the pain disappeared. Injection of ergotamine tartrate reduced the amplitude by about 50 %. At the same time the headache was relieved or disappeared.

In the same way Clark and co-workers (1936) have shown that together with the headache induced by intravenous injection of histamine there came a pronounced increase of amplitude in a. temporalis and that the variations in the headache corresponded closely to those of the amplitude. In other experiments a dilatation in the cerebral arteries of 40—50 % was observed to follow upon injection of histamine.

<sup>1</sup> Personal communication to the author by Professor Mogens Fog.

<sup>2</sup> This explanation seems more plausible than that previously put forward by the author (1942) to the effect that the adequate stimulus was spasms in the arteries released by the increased filling of these.

Clark and co-workers concluded that an increase in the diameter following upon histamine injection was a sign of a reduction in tonus, in which the ability of the vascular wall to react by a suitable contraction to the intravascular variations in pressure was much reduced. Consequently the sensitive end organs in and around the vascular walls were exposed to intense stimulation, this being then felt as pain.

In support of the theory that cardialgia and hunger are released from the gastric arteries it may be stated that Alvarez (1934) who has concerned himself much with the investigation of visceral pain, points out that the viscera and the visceral peritonæum contain but few sensory nerves and that these are closely connected with the arteries.

The anatomical basis is present. Arteries right down to a diameter of 0.5 mm are provided with sensory nerves situated in the outer layer of the adventitia and running in spirals round the vessel. Sensory nerves also wind round arteries of less than 0.5 mm in diameter and round arterioles and capillaries; as a rule, however, they are 20—30  $\mu$  distant from the vessel (Busch 1929).

It may further be mentioned that Gammon and Bronk (1935) have demonstrated the presence of pressosensible nerve-fibres issuing from the mesenterial arteries. On registering action potentials from the peripheral end of the splanchnic and mesenterial nerves volleys of impulses were observed which were synchronous with the pulse. The adequate stimulus to these vascular nerves was precisely a dilatation of the vessel. Changes in the blood pressure only resulted in an increase in the issue of impulses if they involved dilatation of the arteries in question. Thus, for instance, the injection of adrenaline, which made the arteries contract, stopped the issue of impulses, irrespective of the fact that the blood pressure rose, whereas acetylcholin, which brought about dilatation of the arteries and a fall in blood pressure, was followed by a slight increase in the issue of impulses.

Since the vessels of the abdomen are provided with constrictive as well as dilatative nerves, for the stomach by the splanchnic nerves and nervus vagus, it must be taken for granted that the nervously conditioned tonus of the vessels most probably plays a decisive part in the degree of dilatation of the gastric arteries which a blocking of the capillaries in the mucosa is supposed to cause. This

will perhaps explain why the symptoms after the ingestion of adrenaline may vary in nature and intensity.

The explanation of the fact that vigorous hunger contractions, which must be supposed to constrict the gastric capillaries for a short time, give rise to a sensation of hunger in some individuals but not in others, is presumably that a closely adjusted nervous regulation in the latter prevents the constriction of the capillaries following upon the hunger contractions from resulting in changes in the diameter of the gastric arteries producing symptoms. If so, it must be because the hunger contractions release increased sympathicotonus, reduced vagotonus, or both.

No distinct difference could be observed in the mode of reaction in ulcer patients and in normal individuals, except that the ulcer patients did not complain of hunger but exclusively of various dyspeptic symptoms, and that somewhat smaller doses were as a rule given to them than to the normal individuals to produce the symptoms.

In some cases the sensations of discomfort following ingestion of adrenaline recurred several hours later, just as the symptoms now and then persisted beyond the time in which the effect of the adrenaline might be supposed to assert itself. The explanation might be that the dyspeptic symptoms induced by the adrenaline involved a more protracted disturbance, by reflex action, in the tonus of the gastric vessels.

### Conclusions.

The experiments showed that in the majority of cases hunger or cardialgia came on in healthy subjects after peroral ingestion of small doses of adrenaline in 35 % alcohol.

Large doses of nupercaine administered partly before and partly simultaneously with the adrenaline seemed without influence on the onset and intensity of the symptoms.

As an explanation of the mechanism in the genesis of the symptoms the following working hypothesis is put forward:

Adrenaline causes a contraction of the vessels in the mucosa. By retroaction on the arteries leading to the anæmic area these are dilated, and an increase in the amplitude of the pulse in these vessels set in. This stimulates the sensitive end organs in and around the arterial walls, and this is then felt as hunger or pain.

### Summary.

After peroral ingestion of 2 mg adrenaline in 4 cm<sup>3</sup> 35 % alcohol to 6 patients with achylia refractory to histamine dyspeptic symptoms of varying intensity set in 3—8 minutes later. In two cases vomiting occurred, and in one case excessive hunger.

A single or up to three times repeated ingestion of 3 mg adrenaline in 6 cm<sup>3</sup> 35 % alcohol produced either hunger or cardialgia, or both, in 18 out of 20 healthy subjects. 4 of the subjects grew so hungry that they did not remember ever having felt a similar hunger before.

Ingestion of 5 cg nupercaine 5—10 minutes before the administration of adrenaline, or ingestion of adrenaline in a 1 % solution of nupercaine hydrochloride did not prevent the onset of the symptoms which apparently set in with the same intensity.

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From the Department of Psychiatry, Karolinska Sjukhuset, Stockholm.

## Disturbance of Circulation in Convulsions of the Epileptic Type.

### I. Intrathoracic and intra-abdominal pressure during electroshock.

By

T. GORDH and B. P. SILFVERSKIÖLD.

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The pressure changes in the thorax during convulsions of the epileptic type have previously been studied through animal experiments (Schmitterlöw and Silfverskiöld 1943). Marked elevations in pressure were then recorded. The experimental conditions were not so good, however, as to allow of an exhaustive investigation on the pressure variations. The electrically induced convulsion has the characteristics of an epileptic attack, and the clinical electroshock provides good opportunities for an experimental study on these pressure relationships. This paper describes an investigation made on the pressures in the thorax and the abdomen by means of measurements in the oesophagus, the trachea and the ventriculus.

*Method.* The experiments were carried out during the ordinary electroshock treatment. For the most part, the subjects were young men, but a few determinations were done on young women. — A thick cushion was placed under the patient's back, and his shoulders were pressed downward during the convulsive attack. This measure, as we shall see further on, may have an influence on the result.

A bulb of thin rubber having a capacity of about 10 cm<sup>3</sup> was attached to an ordinary duodenal cannula. For the measuring of the intrathoracic pressure the bulb was introduced into the oesophagus (for a distance of

30 cm from the teeth), and to obtain the abdominal pressure it was introduced into the stomach (for a distance of 60 cm from the teeth). During the firstmentioned procedure a tendency toward oesophageal contractions was evidenced, and in order to avoid this the bulb was inflated, before the experiment, only by means of the negative pressure in the thorax (in the way described by Nordenfelt, 1934). As regards the stomach, there was obviously no risk of contraction, and the bulb was therefore blown up to a pressure of about 10 mm of mercury. The cannula was then attached to a small aneroid manometer which was capable of registering both positive and negative pressures.

After the convulsion the bulb was withdrawn — still connected with the manometer — and manually compressed. By this means it was possible to control that the bulb had been sufficiently full of air to produce a pressure higher than that measured during the attack. If this was not the case, the experiment was rejected.

The pressure was read off from the manometer every five seconds; this interval sufficed to record all variations of importance. Extra readings were made when necessary.

*Results.* The pressure alterations in the oesophagus were as a rule relatively slow and easy to follow during the tonic phase, after the initial rise. During the clonic phase, there were in some instances fairly strong fluctuations which kept pace with the muscular spasms.

The intra-oesophageal pressure during the convulsion was of different types. In some cases a very high pressure, up to as much as 110 mm of mercury, was recorded during the tonic phase. Judging from our thirty experiments, it would seem as if the pressure often rises to about 80—100 mm in men. In a not-inconsiderable number of cases, however, a definitely negative pressure was recorded. In all probability the pressure was positive when the chest was expanded at the start of the convulsion, and negative when there had been an expirium just before the onset of the attack.

In many instances the electric stimulus was given systematically when the thorax was either in the position of expiration or of inspiration. In some of these patients it was possible by this means to cause the convulsion to begin with the chest either in expiration, or inspiration, respectively. In respect of the first-mentioned phase, there were small elevations in the intrathoracic pressure and at times it showed a moderate minus value. With the chest expanded, on the other hand, there was a marked increase in the pressure. (Figure I presents a few typical pressure curves.) The part played by the position of the thorax at the onset of the convulsion was also brought out by pneumography. — It may be mentioned that some patients obviously had a stronger tendency to go into convulsion with

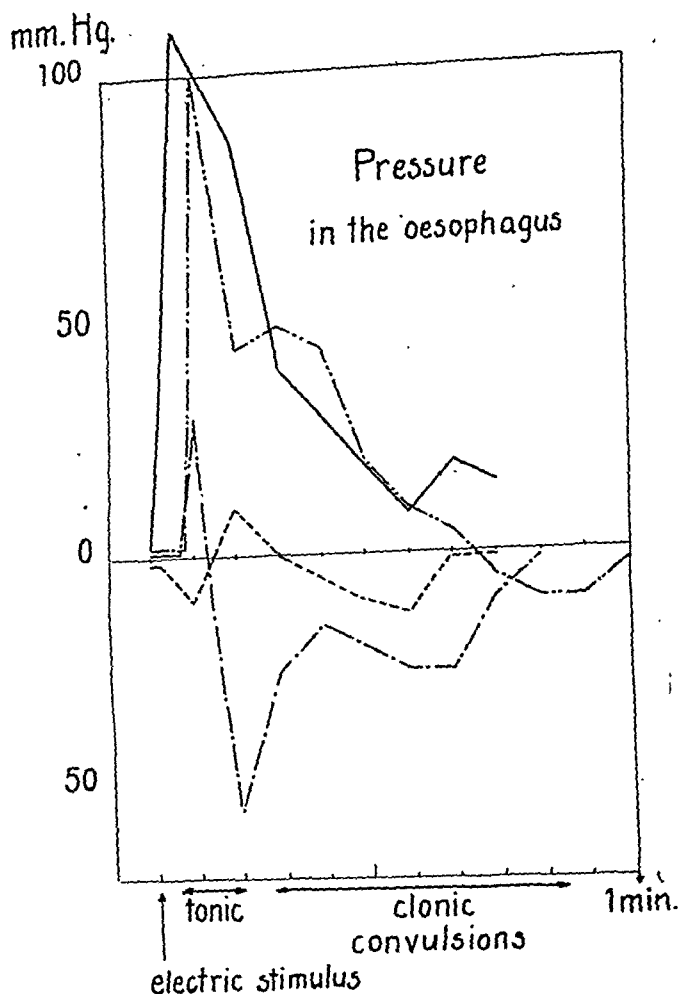


Fig. I.

the thorax expanded than others, and that in these instances a leaning toward strong positive intrathoracic pressures was thus in evidence.

This difference in pressure in regard to the expiratory and inspiratory positions must depend upon the fact that the intra-oesophageal pressure is an expression of the intrathoracic pressure, and it may thus be inferred that the recordings from the oesophagus can be used for the study of the pressure in the thoracic cavity. The possibility that oesophageal spasms may somewhat distort the results, and that the high positive pressure will thus be due, at least in part, to powerful oesophageal contractions, must of course be borne in mind.

We endeavoured to determine the intrapulmonic pressure, however, and by so doing to find an answer to this question.

*Method.* After a pantocain spray of the throat and the trachea, a rubber tube of the type used for intratracheal anesthesia in operations on the lungs was inserted orally with the assistance of a laryngoscope. An inflated rubber cuff applied around the distal end of the tube ensured an absolutely airtight passage to the lungs. The upper end of the tube was attached by means of a y-tube to a manometer and also to a valve. The valve was only connected at the onset of the convulsion. The attack often started with an inspiration which was made possible by the valve. During the convulsion, expiration was prevented by the valve, which thus played the same inhibitory rôle against expiration as cramp of the glottis during a natural electroshock. While this arrangement did not fully correspond to the natural conditions, it was possible to obtain comparative values between the intratracheal pressure and the simultaneously measured oesophageal pressure.

The pressure in the *trachea* during an electrically induced convulsion was found to be quite as great as the highest pressure simultaneously or previously recorded in the oesophagus. More detailed comparisons could not be obtained, however, as the measurements on the trachea were inclined to be uncomfortable for the patients and to cause them to fear even the ordinary shock treatment.

It was fairly evident, however, that oesophageal spasms could not have had any great share in producing the high intra-oesophageal pressure values which were recorded.

Thus, high pressures may occur in the thorax. A condition resembling a Valsalva's experiment is therefore brought about by an induced convulsion. We shall return further on to the significance of this feature.

Figure II illustrates the usual appearance of the pressure tracings from the *ventriculus* during an induced convulsion. It will be seen that the pressure rose to a high level during the tonic phase. The mean pressure then dropped slowly during the clonic phase, with violent pressure variations which have been sketched in with a broken line. We made about twenty experiments on the intra-abdominal pressure, and found that in young men the pressure seems to rise as a rule to between 150 and 220 mm of mercury. The pressure elevation in women was on the whole about 70 mm lower.

That the increase in pressure and the subsequent variations took place in perfect rhythm with the different phases of muscular activity could be readily controlled. It was unthinkable that the rapid, violent pressure changes could have been due to stomachal contractions.

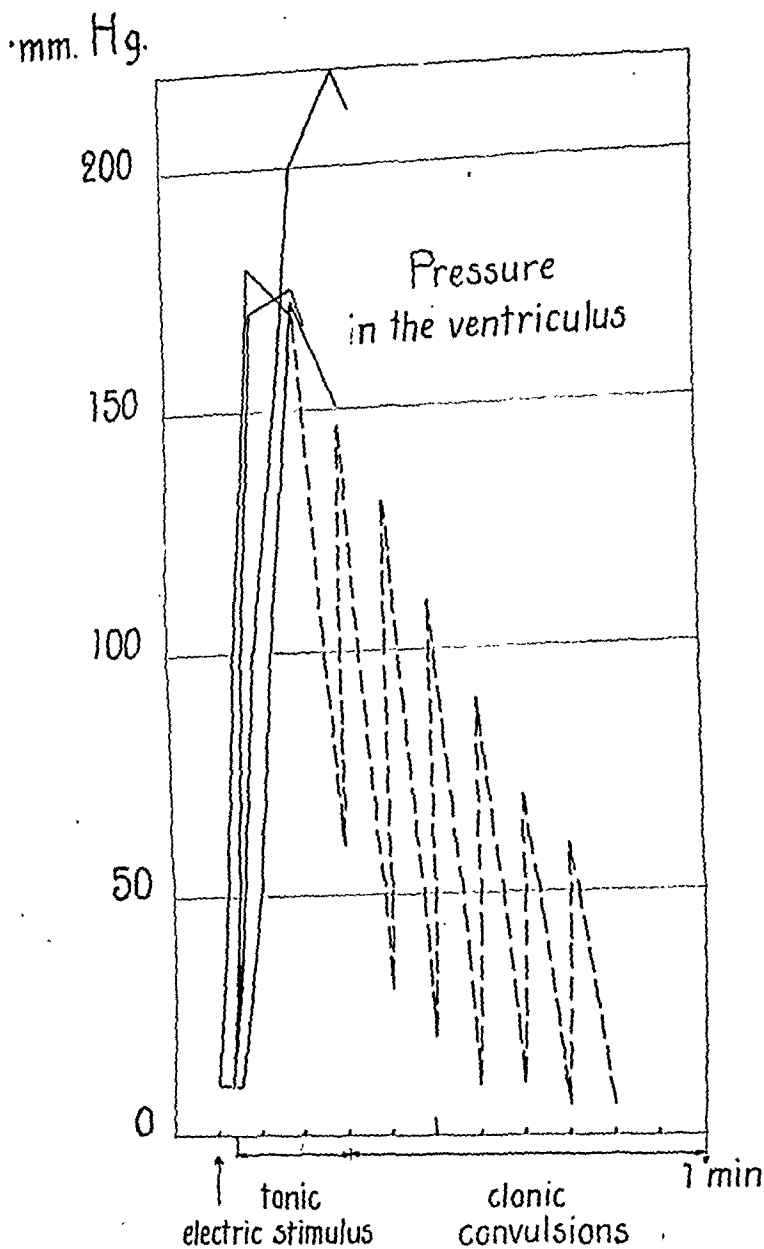


Fig. II.

The latent period very likely has some effect on the pressure curve, both as regards the intrathoracic and the intra-abdominal pressures. The convulsions are not directly brought on by the electric stimulus, as is evidenced by the fact that, with a moderate convulsive dose, the attack begins a short time after the stimulus has been discontinued. Particularly after a latent period lasting longer than about five seconds, the onset of the convulsion is gra-

dual, thus having a closer resemblance to the spontaneous epileptic attack. The slower initial rise in pressure in attacks following a latent period is illustrated by one of the examples in figure II. With no preliminary latent period, such as is the case after an over-dose, the attack sets in abruptly, directly after the application of the stimulus, a fact which is reflected in the pressure tracings. This probably is the explanation of the fact that the attacks induced by over-doses seem more dangerous than those preceded by a latent period.

The intra-abdominal pressure in all probability reaches the same high level irrespective of whether or not a latent period precedes the attack. The high intrathoracic pressures, on the other hand, probably occur more often in connection with the more abrupt attacks; the reason for this is that in these a strong inspiration is generally seen to occur before the convulsion. This preliminary inspirium appears to be a prerequisite for a high positive pressure.

*Discussion.* It is possible that the pressures in the thorax and the abdomen were higher in our experiments owing to the position of the patient. By placing a cushion under the back the chest becomes expanded and the muscles of the anterior abdominal wall are stretched. This position, however, does not diverge to such an extent from the spontaneous position seen in induced convulsions that the difference in pressure need be attributed much significance. The pressure changes described in this paper may therefore be presumed to be a good illustration of the pressure variations occurring during an epileptic convulsion induced by an electric stimulus.

By studying these pressures, we may gain an idea of the strength of the induced convulsion, (and follow the effect of different methods of moderating the attacks), and we may also learn something of the possible influence exercised by the intra-abdominal and intrathoracic pressures on the circulation. In a Valsalva's experiment there occur appreciable changes in the circulation despite the fact that the intra-abdominal and intrathoracic pressures do not generally reach higher values than 60—70 mm of mercury. In an electrically induced convulsion the intra-abdominal pressure reaches a many times higher figure, and in some instances high intrathoracic pressures are recorded. We may assume therefore that in the in-

duced convulsion marked disturbances of circulation result from the great increases in pressure in the body cavities. Disturbances must arise, for instance, through the compression of the arteries and veins in the abdominal cavity due to the intra-abdominal pressure, and through the fact that the pressure in the thorax affects the return venous flow to the heart.

A preliminary reference to the resemblance of a Valsalva's experiment to an induced convulsion was made by Silfverskiöld in 1911, and an investigation on disturbances of circulation is to be published shortly (Silfverskiöld and Åmark 1943). It has been suggested in these papers that a general lessening of the arterial flow to the periphery may occur as a result of a decrease in the stroke and minute volumes of the heart.

From the clinical point of view, the question of whether it is better to give the electric stimulus with the thorax in inspiration or in expiration is of interest. The latter position seems to be the more advantageous. We carried out a few tests on the relationships not only of the intrathoracic but also of the intra-abdominal pressure, and it was found that the pressure possibly increased less abruptly when the stimulus was applied in the expiratory position. As we have already mentioned, however, the patient often takes a deep breath at the onset of the convulsion — particularly if the latent period has been short — and expectations of good results from this method should therefore not be too high. The chief precautionary measure, when a not too violent onset is desired, is to give a suitable dose. A natural and, from the standpoint of both circulatory system and skeleton, a less dangerous convulsion is thereby produced.

### Summary.

The intrathoracic and intra-abdominal pressures during electrically induced convulsions were obtained by measuring the pressure in the oesophagus, the trachea and the ventriculus.

The intrathoracic pressure varied markedly during the convulsions. For the most part, positive pressure values, in some instances very high, were recorded, but moderate negative pressures were often noted.

The intra-abdominal pressure invariably rose to a high level during the tonic phase (up to 220 mm of mercury in men).

These strong pressure changes may be presumed to cause considerable disturbances of circulation similar to those believed to occur during Valsalva's experiment.

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## Disturbance of Circulation in Convulsions of the Epileptic Type.

### II. Arterial and venous pressure during electroshock.

By

B. P. SILFVERSKIÖLD and C. ÅMARK.

(Submitted for publication October 28, 1942.)

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Up to the present time, no study appears to have been made of the arterial and venous pressure in man during convulsions of the epileptic type. Animal experiments, as mentioned in another paper (Schmitterlöv and Silfverskiöld 1943), can hardly provide any conclusive, quantitative idea of blood pressure relationships in the human convulsion, and we have therefore undertaken an investigation on the pressure in the arterial and venous systems in convulsions induced by electric shock. The records were made by means of the direct method. For obvious reasons, the rubber cuff or any similar method could not be employed. When the work was started it was thought unlikely that good values could be obtained under such difficult conditions as those prevailing during violent convulsions. Many of the experiments certainly did fail, but a fairly large number of measurements were nevertheless obtained. This was in large measure due to the simple and easily handled method which was used, and of which a description is appended.

*Method.* A hypodermic needle with a caliber of about 2 mm was connected by means of short rubber tubing joints and an ordinary Westergren SR tube with a small aneroid manometer. A couple of drops of a 5 per cent

solution of heparin were injected into the needle. A cubital vein, or the cubital part of the brachial artery, was then punctured. The majority of the subjects chosen were men, as it was found that only in men could reliable punctures be made: In the case of sensitive patients, a little novocain blister was placed at the site of the puncture. The cubital fossa was held at a level a couple of centimeters below the sternum and the manometer somewhat higher. In some instances a column of blood rose in the glass tube. When this occurred the height of the column was worked out in millimeters of mercury and added to the manometer value.

The blood pressure in the vena jugularis superficialis dorsalis (external jugular vein) was measured in another series.

The pressure curve rose and fell continuously in most of the patients, and it was therefore sufficient for our purpose to make a manometer reading every five seconds. Extra readings were made when necessary.

The determinations were carried out while the patients were undergoing the ordinary electroshock treatment. Before the shock the patients were made to inhale oxygen for about one minute. This may be of significance, as the asphyxia produced by the shock was lessened by this measure.

*Results.* The pressure in the cubital vein rose invariably to very high values; 100 mm of mercury, or a little over, was measured in several instances. As a rule the pressure rose fairly rapidly to its maximum during the tonic phase, and sank back gradually during the clonic phase. The starting value was often reached just at the end of the attack, but in some instances the pressure remained raised even after the convulsion. We observed that the pressure in the cubital vein varied by 30—40 mm of mercury according as the arm was in a more or less lateral position during the convulsion, and also that it rose to a high level in some of the patients showing no increase in the intrathoracic pressure. We therefore suspected that the rise in pressure might depend to a certain extent on a local disturbance of circulation in the veins of the arm.

As the venous pressure in the head was considered to be especially interesting in this connection, we made a study of the pressure in the external jugular vein. There was no danger of air embolism occurring as the system by which we obtained the recordings was a closed one. The vein in question is not particularly accessible to puncture, especially with a needle as thick as the one we employed, but we succeeded in obtaining tracings from ten patients.

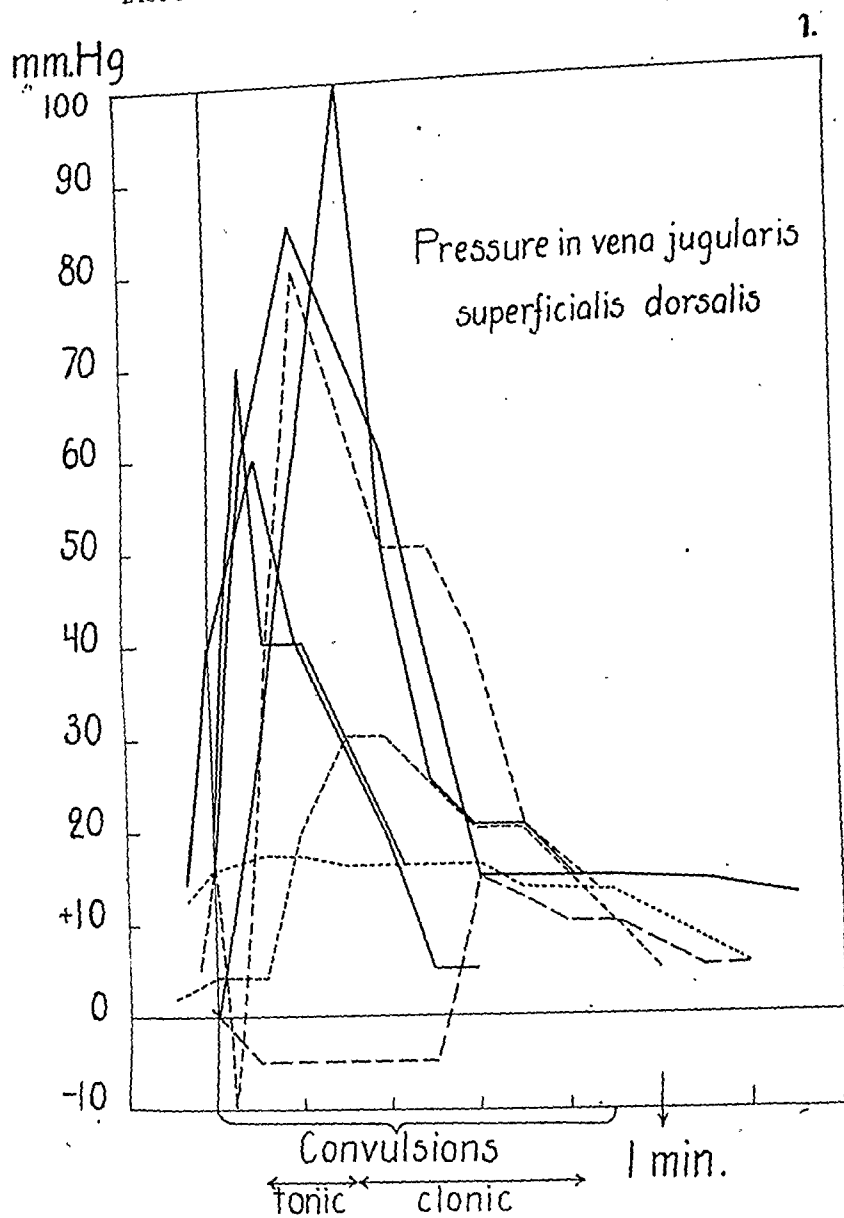


Figure I illustrates that the pressure in the vein of the neck increased to a marked degree in some of the patients. In others the rise was slight, and in one it was even negative. In three patients the electric stimulus was given when the chest was in the position of expiration, and in the others when the chest was expanded. The pressure was seen to be distinctly lower in the first-mentioned three patients than in the others. According to the observations made during an investigation on the pressure relationships in the thorax

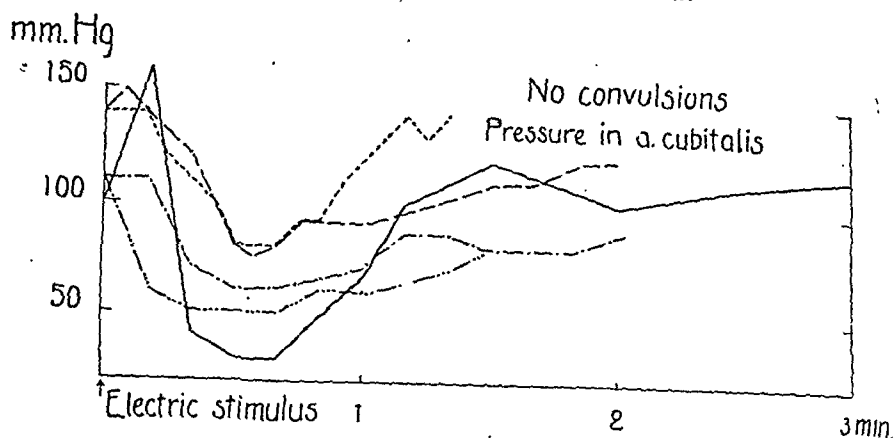


Fig. II.

(Gordh and Silfverskiöld 1943), the intrathoracic pressure increases markedly only on condition that the convulsion begins when the thorax is in the position of inspiration, and it therefore seems logical to assume that the venous pressure only rises in patients displaying an increase in the intrathoracic pressure.

The pressure rise in the external jugular vein seemed to be of fairly short duration, and in some of the patients it even returned to the starting value before the end of the convulsion. In this respect it differed from the pressure in the vein of the arm, which sometimes remained raised even after the attack had come to a close.

The arterial pressure was measured both after subthreshold stimuli and during the course of a convulsion. A total of fifteen recordings were made on the arterial pressure during a convulsion, and ten after the application of subthreshold stimuli.

Figure II provides a few examples of the fact that the electric stimulus, when it is not followed by a convulsion, tends to cause a decrease in the arterial pressure. This drop is often considerable. In the ten determinations we made, the pressure values fell by 20–70 mm of mercury. In one instance a figure as low as 30 mm was obtained. In spite of the drop evidenced in these patients there were no signs of a serious collapse. Everyone who has worked with the electroshock treatment knows, however, that severe, though not serious, collapse can result from stimuli of this kind. In all probability, the subthreshold stimulus has a fairly strong tendency to bring about a fall in the arterial pressure. — A high

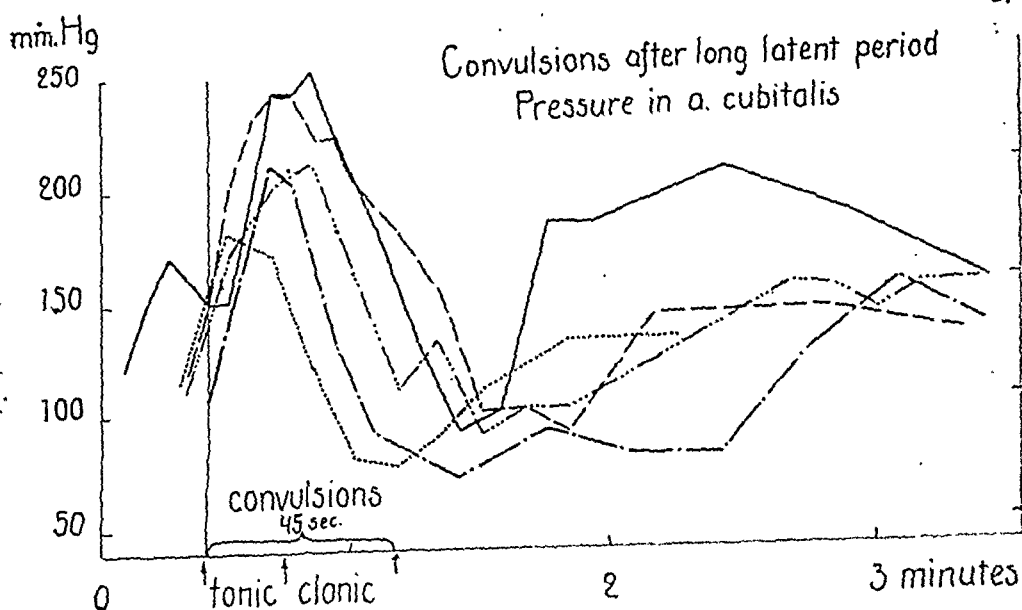


Fig. III.

degree of bradycardia was also noted in connection with the fall in pressure.

As is well known, when the dose has been suitable the convulsive attack does not begin until a short time after the electric stimulus has been discontinued. There is sometimes a preliminary latent period lasting some tens of seconds. In figure III there are shown tracings of the arterial pressure in attacks following upon a latent period of fairly long duration. The pressure rose a little in some instances during the latent period, which was often characterized by a moderate degree of muscular tension. As soon as the tonic phase of the convulsion set in, however, the arterial pressure rose to a high level. In two cases the value recorded was 240—250 mm of mercury. During the clonic phase there was a fairly rapid drop. After the convulsion was over, the pressure sometimes fell below the starting value and then slowly increased again to a point above the original level. After a further few minutes, the normal relationships had generally been re-established.

Figure IV presents tracings from convulsive attacks which were preceded by no appreciable latent period. In these the pressure rose abruptly to approximately the same high levels as those described above, receding subsequently in a quick drop and then rising again a second time, as was the case in figure III. — It may be mentioned

mm. Hg

250

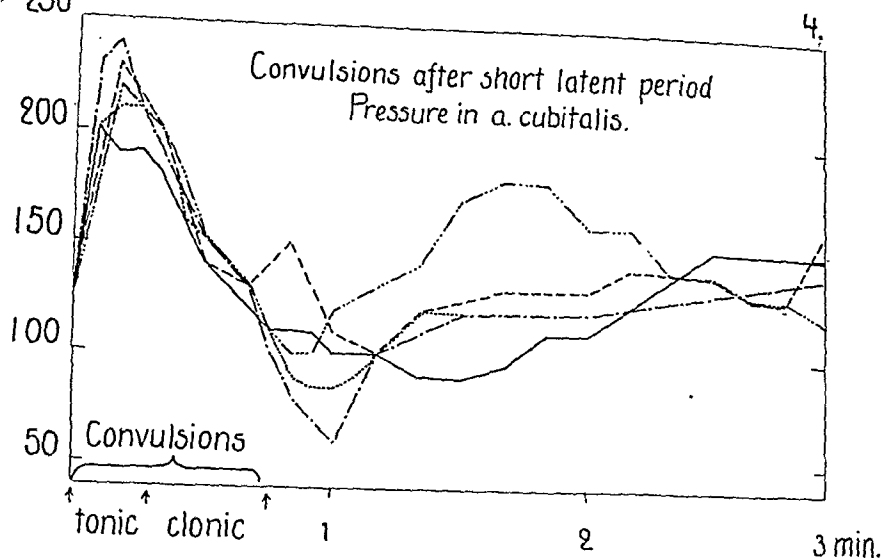


Fig. IV.

that the arterial pressure rose in the usual way in a couple of the patients in whom the intrathoracic pressure was not increased.

The method naturally does not lend itself to a study of the finer aspects of blood pressure relationships. Of greatest interest, however, was the fact that while the usual pulse wave oscillations were recorded by the manometer before and after the convulsion, there was practically no indication of any pulse wave fluctuations during the attack. We shall return further on to the lessening of the pulse wave, which must be the reflexion of a considerable decrease in the stroke volume of the heart.

The pulse rate could not be measured, and the heart rate was therefore studied instead, by auscultation. It was found that the heart tones disappeared during the first few seconds of the tonic phase, and then appeared again with gradually increasing strength. As long as the tones were audible mild tachycardia was present. When the clonic phase set in, auscultation was impossible because of the commotion made by the muscular spasms. We were not able to determine whether the short absence of the heart tones was due to a pause in the heart beat, but we hope to return to this problem in a later investigation.

*Discussion.* The observations made during this investigation prove that a violent disturbance of circulation occurs during convulsions. Both the arterial and the venous pressure show a marked increase. It would seem as if such high blood pressures must surely be dangerous for the heart and the brain. In practice, however, it has been found that disasters traceable to disturbances of the heart do not occur even in fairly debilitated patients. The reason for this must be that there is no great increase in the work of the heart. As for the brain, rupturing of the blood vessels is in all probability counteracted by a simultaneous rise in the cerebrospinal fluid pressure. It was our intention to make a series of determinations on the cerebrospinal fluid pressure, but we gave up the idea after a couple of experiments, on account of the risks that were involved. Our first experiment was successful, however, and the high value of 135 mm of mercury was recorded. Earlier workers who have measured the cerebrospinal fluid pressure in cardiazol shock also obtained very high values (Niketić and Sušić 1938; Valso 1939). It may be assumed therefore that in convulsions, as in violent coughing, sneezing, or straining, the pressure rises strongly, and thus relieves the strain on the walls of the encephalic blood vessels.

As already mentioned in previous communications (Silfverskiöld 1941; Schmitterlów and Silfverskiöld 1943; Gordh and Silfverskiöld 1943), the picture in convulsive attacks resembles that seen during Valsalva's experiment. The rise in the abdominal pressure and, to a certain extent also, in the intrathoracic pressure, is much higher during convulsions, however.

The relationships occurring during Valsalva's experiment have been studied very thoroughly (see Liedholm 1939), and it has been found that besides a powerful rise in the arterial, venous, and cerebrospinal fluid pressures there also occurs a definite lessening of the stroke and minute volumes of the heart (Böger 1932; Wezler and Knebel 1939). The minute volume may be decreased by as much as 50 per cent or more.

During convulsions of the epileptic type the pulse disappears, as it does on occasion during Valsalva's experiment. As we have pointed out earlier in this paper, this diminishing of the pulse is reflected, in the measurements on arterial pressure, in the fact that the pulse oscillations are on the whole absent during the convulsion. This circumstance must be indicative of a very considerable lessening

in the stroke volume, and evidently also in the minute volume, a lessening which is in all probability even greater than that which occurs in Valsalva's experiment. (This refers to the greater part of the convulsion. During the first few seconds of the attack there possibly occurs instead a total stop in the heart beat, and during these seconds, as will be described below, mechanical displacements of the blood due to the muscular contractions probably take place.)

One of the reasons why this point is of particular interest is that in the past a great many workers have found that brain lesions arise after epileptic convulsions. These lesions have been regarded, by Spielmeyer's school in particular, as being due to a local contraction of arteries and the resultant nutritional disturbances in the brain tissue.

In our opinion, there may occur a decrease in the blood flow to the periphery in electrically induced convulsions, and in all probability in all convulsions of the epileptic type. This decrease might depend upon a reduced stroke and minute volume, (and on stasis in the veins). The brain lesions might therefore be caused by a general lessening in the blood flow to the periphery in conjunction with the convulsion apnea.

The decrease in the flow of blood to the periphery must here be associated with general arterioconstriction, and the high arterial pressure may be due in part to contraction of the arteries. In all probability, however, this contraction has a small share in the genesis of the reduced blood flow.

We do not intend to enter into a detailed discussion on the cause of the disturbance of circulation arising in connection with the large increase in intrathoracic and intra-abdominal pressures. It should be pointed out that the circulation relationships are extremely complicated. However thorough the studies on Valsalva's experiment may have been, it is doubtful whether all the relevant factors can have been taken into consideration. The high abdominal pressure, however, which sometimes rises to over 200 mm of mercury and therefore may be presumed to bring about considerable compression of the abdominal vessels and consequently cause an initial large rise in the arterial pressure, is of particular interest from the point of view of the physiology of the circulation in convulsions. The fact that con-



currently with these intra-abdominal pressure values there may occur low, even negative, values for the intrathoracic pressure must also be of importance. There is reason to believe that the abdominal pressure is of greater significance than the intrathoracic. The lessening in the stroke volume may be considered to be dependent to a large extent upon a diminishing in the return flow of the venous blood. This decrease in the return venous flow may occur, however, through stasis of the blood in the extremities, even when there is no increase in the intrathoracic pressure. The abdominal pressure must always be accompanied by venous stasis in the legs, and, as the experiments described in this paper demonstrate, venous stasis in the arms may also occur in convulsions without any rise in the intrathoracic pressure.

The disturbance of circulation which occurs in connection with electroshock convulsions may also be of clinical interest. If cerebral changes are brought about through this disturbance, great restraint ought to be exercised when subjecting patients suffering from psychic illness to electroshock therapy, particularly in view of the fact that mild brain damage has been demonstrated in animal experiments (Cerletti and Bini 1940). In reality, however, the possibility that cerebral lesions might arise has been borne in mind from the beginning, and the reason why electroshock treatment is now being given to patients with milder forms of psychic illness is that no lasting clinical signs of brain damage have been observed even after relatively intensive treatment. Furthermore, persons doing qualified intellectual work have also been able to resume their occupation after the treatment without noticing any difference in the quality of their work when compared with the period before their illness. It should nevertheless be remembered that in electroshock therapy as few treatments as possible should be given.

### Summary.

The arterial and venous pressures occurring during electroshock convulsions have been obtained by the direct method.

A marked rise was observed in both the arterial and the venous pressure.

During the entire convulsion the pulse wave oscillations were absent. This suggests that a definite lessening in the stroke volume of the heart takes place.

On account of the decrease in the stroke volume, and the consequent decrease in the minute volume, a general lessening of the arterial blood flow to the periphery probably occurs during the convulsion. This may be an explanation of the ischemic brain lesions occurring in epilepsy.

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(From the Medical Department of Serafimerlasarettet, Stockholm. Chief: Professor A. Kristenson, and from the Neurologic Department of the same hospital, Chief: Professor N. Antoni.)

## Fractioned Testing of the Carbohydrate Metabolism in a few neurologic cases.<sup>1 2</sup>

By

GRETA HAMMARSTEN and ERLAND MINDUS.

(Submitted for publication October 29, 1942.)

Deficiency of vitamin B has been blamed for many diseases in the nervous system, and numbers of successful therapeutic results have been published. But, despite extensive research, very little is known of the relationship between vitamin B factors and neuropathologic conditions, and agreement has not been reached as to what neurologic diseases are really due to a vitamin B deficiency. One of us (M) recently gave an account of the unsolved problems in connection with a review of the published therapeutic results. One of the explanations of the many obscure points is that the diagnostic possibilities in vitamin B deficiency are inadequate. Another explanation is the confusion between the general tonic effect of vitamin B and its more specific action on the nervous system.

Carlström, Myrbäck, Holmin and Larsson (1939) were the first in Sweden, as far as we know, to have studied the question of the part played by aneurin deficiency in the carbohydrate metabolism in nervous diseases. These writers described a case exhibiting paresis and muscular atrophy, in which, in addition to determination of

<sup>1</sup> This paper was read at a meeting of the Swedish Society of Internal Medicine on January 30, 1942.

<sup>2</sup> The expenses of this investigation have been defrayed in part by the Johan och Therese Anderssons Minnes Foundation.

the pyruvic acid in the blood, the contents of bisulfite-binding substances, lactic acid, total acetone and  $\beta$ -oxibutyric acid were also measured. All the values were high, but dropped to normal as the condition of the patient improved following treatment with aneurin.

In cases in which a disturbance in the carbohydrate metabolism was suspected, one of us (H) has made glucose tolerance tests, carried out with special regard to the function of the vitamin B group and the magnesium in the intermediate carbohydrate metabolism. The investigation was conducted according to the following plan in neurologic cases:

1). Determination of the pyruvic acid content in the blood (according to Lu, modification by Löfgren. The normal values at rest did not exceed 1.2 mg per 100 cm<sup>3</sup> ( $\sigma = \pm 0.1$  mg per cent.)

2) If the value for pyruvic acid was increased, an ordinary glucose tolerance test was made with the administration of 1 gm of glucose per kilogram of body weight. The patient was preferably given an extra supply of carbohydrates a few days before the test was made. Immediately before the administration of glucose a sample of capillary blood was taken for the determination of sugar and pyruvic acid. Thereafter the blood sugar was tested every 20 minutes for the first hour and then every half hour for the following two hours. Pyruvic acid determinations were carried out every hour. Since pyruvic acid is a precursor to citric acid, the content of the latter substance in the venous blood was determined in some cases, sometimes with the patient fasting and sometimes during the course of the tolerance test. The administration of vitamin B was begun immediately after the first tolerance test (1 to 2 Ml. daily of the preparation »Injectab. B. comp. Serafen», from the pharmacy, Lejonet. 1 Ml contains 0.010 g of aneurin, 0.0005 g of lactoflavin and 0.010 g of nicotinic acid amide). At the same time, or possibly after a second tolerance test, magnesium was given (1 teaspoonful three times daily of a mixture of tricalcic phosphate  $[\text{Ca}_3(\text{PO}_4)_2$  88 and magnesium oxide ( $\text{MgO}$ ) 20]. Three to six days later another glucose tolerance test was carried out, together with determinations of pyruvic acid.

The above method has been used in several cases observed at the Neurologic Department of this hospital. Three of these cases exhibiting disturbances in the carbohydrate- $\text{B}_1$ -metabolism will be described herein. The patient in Case 1 had polyneuritis due to impaired resorption in connection with chronic ileus. Case 2 was one of myelopathy in which the patient had a short period of confusion and suffered from gastritis and cirrhosis of the liver. In Case 3 the patient had neuralgia-like pains in the face and exhibited

recurrent colitis with impaired resorption of vitamin C. All three cases showed aneurin deficiency and a disturbance in the carbohydrate metabolism, expressed as raised pyruvic acid values in the blood and possibly a blood sugar curve broader than normal. Treatment with vitamin B had a favorable effect on these signs, particularly when the treatment was complemented by the administration of magnesium. Some improvement was also noted in the neurologic symptoms, the pain and parasthesias being affected first, while the motor changes remained so long in the first two cases that the connection between vitamin B deficiency and the symptoms was no longer quite clear.

### *Case Histories.*

No. 1. B. I. F. 29-year old officer, hospitalized since November 20, 1941. Record No. 1006/41.

*Family history:* The patient's mother died of an unspecified gastric disease. Otherwise the heredity was of no interest.

*Previous diseases:* In 1934 the patient spontaneously passed a kidney stone. Apart from his gastric disease, he had always been healthy. There was no history of alcoholism or venereal disease. The patient used to be a good athlete. He always had stomach trouble, with diarrhea alternating with constipation and a great deal of flatulence. In September he began to have vomiting, raising thin, yellow-green matter. Food never directly disagreed with him, but he always had particularly troublesome flatulence after eating fruit and vegetables. There was no abdominal pain, but some tenderness when the flatulence was especially severe. His appetite became poor and he lost weight, altogether about ten kilograms from June 1941. He became increasingly tired and finally scarcely had the strength to walk up a flight of stairs. During this period he noticed no pain or numbness nor any weakness of the hands or feet beyond the sensation of general weakness.

The patient was admitted to the Surgical Department of the Military Division of Karolinska Sjukhuset on October 9, where his condition was diagnosed as megaduodenitis. He was pale, haggard and very thin and looked tired and lacking in energy. The abdomen was soft, retracted and non-tender and no growths could be palpated. Ewald's test meal was fairly well digested. The mucus was graded II to III. The value for free hydrochloric acid was 4; for total acidity, 19; and for total volume, 77. The stools were pale brown and formed and exhibited no muscular remnants, scanty fat drops, and no iodophil substance. The peroxidase index was 9. The Weber reaction was negative. The diastase test gave the value 16. The blood and urine were normal. Roentgen revealed the stomach and duodenal bulb to be normal. The duodenal loop was dilated to the width of

an arm and was full of fluid. A stenosis was found in the region of the duodenojejunal flexure, through which the contrast fluid passed sluggishly. There was extensive retention in the duodenum after four hours. Due to a considerable admixture of fluid, it was not possible to secure satisfactory filling of the site of the stenosis, the exact configuration of which was poorly reproduced. No growth corresponding to the intestinal obstruction could be palpated.

Laparotomy was done on October 21 (Palmér), since the most reasonable diagnosis appeared to be high chronic ileus. A tremendously dilated, thin-walled duodenum was exposed. Around the duodenojejunal flexure, by the passage of the vessels over the intestine, was found a cluster of soft, plum-sized glands, one of which was excised (microscopic diagnosis: non-specific adenitis). Nothing else of interest was found. A duodenojejunostomy was done. Retrograde colonic examination made shortly afterward revealed that the colon was considerably wider and longer than normal, presenting the picture of atony.

On November 11 the patient was allowed up, but complained of weakness in the legs, which also felt numb and powerless. Examination disclosed that the legs were greatly emaciated, that the gait was clearly ataxic and that active flexion of the toes was impossible. The knee-heel test was carried out somewhat clumsily on both sides. The surface as well as the deep sensibility was reduced in both legs. The muscular reflexes in the legs were lacking. There were no symptoms from the arms, except for slight pain in the upper left arm. The patient now became hoarse which, according to the examination, was due to a functional paresis of the vocal cords. Examination of the spinal fluid revealed nothing pathologic. Because of a somewhat sluggish response to the Queckenstedt test, gas myelography was carried out, but disclosed nothing of note. The serologic reactions were normal.

Upon admission to the Neurologic Department the patient looked emaciated and asthenic. The internal organs showed nothing of real interest. The patient's appetite was good and he was able to eat ordinary food. A fractionated histamine meal showed a maximum total acidity of 55 and normal secretory volume. The blood and urine were normal. Bilirubin, 0.12 mg per cent; ascorbic acid in the urine, 1.3 mg per cent. — Mental examination revealed nothing beyond a certain degree of fatigability.

Neurologic examination: The cranial nerves were normal with the exception of a mild bilateral paresis of the vocal cords (hoarseness). The strength of the arms was relatively good, but that of the knee and foot joints was considerably reduced. Dorsal flexion in the toe joints was completely lacking. The patient could not sit up from the supine position without support. The muscles of the thighs and lower legs were greatly atrophic. Histologic examination of a biopsy specimen from the right quadriceps muscle (Docent Wohlfart) showed non-characteristic muscular atrophy. The superficial parts of the specimen showed signs of inflammatory irritation, probably of a local nature. The intramuscular nerve trunks

was also instituted. On January 25, 1942, the general condition was good, the hoarseness was gone, there was no difficulty in walking, and the toes could be flexed dorsally. In addition the deep sensibility was good and the surface sensibility was improved. The muscular reflexes were unchanged. There was no more pain in the left upper arm or in the legs. The same treatment was continued. Control tests of glucose tolerance and pyruvic acid concentration on January 21 gave normal values (fig. 1 d).

*Summary and discussion.* A 29-year old officer with a heredity of gastric disease had always been troubled by constipation alternating with diarrhea. In 1938 the condition grew worse for a time but improved with diet. In the summer of 1940 the symptoms returned and became increasingly severe. The patient had constant intense flatulence, lost weight and felt weak and tired. In September 1941 he began to vomit thin material. The loss of weight continued and finally the patient was hospitalized under the diagnosis chronic ileus. Examination on admission revealed considerable dilatation of the duodenum with stenosis in the duodenojejunal flexure as well as atony of the colon. These findings were verified by an exploratory laparotomy. Duodenojejunostomy was done. After the operation the feet became paretic and numb. The patient was referred to the Neurologic Department for observation. Here he was found to be emaciated and to present the picture of polyneuritis with motor and sensibility changes, as well as impaired reflexes. The spinal fluid was normal. Gas myelography revealed nothing pathologic. Glucose tolerance tests and estimations of the pyruvic acid and nicotinic acid showed an impaired carbohydrate metabolism (a somewhat delayed glucose reaction, high blood pyruvic acid values, low nicotinic acid excretion values). During treatment with vitamin B (Becozym) and magnesium salt, the symptoms regressed, the pyruvic acid values returned to normal and the glucose tolerance proceeded normally. The poorest reaction was observed in the excretion of nicotinic acid.

In all probability this patient suffered from a congenital disturbance in the digestive apparatus affecting principally the duodenum, but involving the colon to some extent also. The condition most closely resembled Hirschsprung's disease. Chronic ileus developed, possibly through various foci of adenitis, and the impairment in intestinal resorption dependent on the ileus was probably responsible both for the vitamin B deficiency and the polyneuritis.

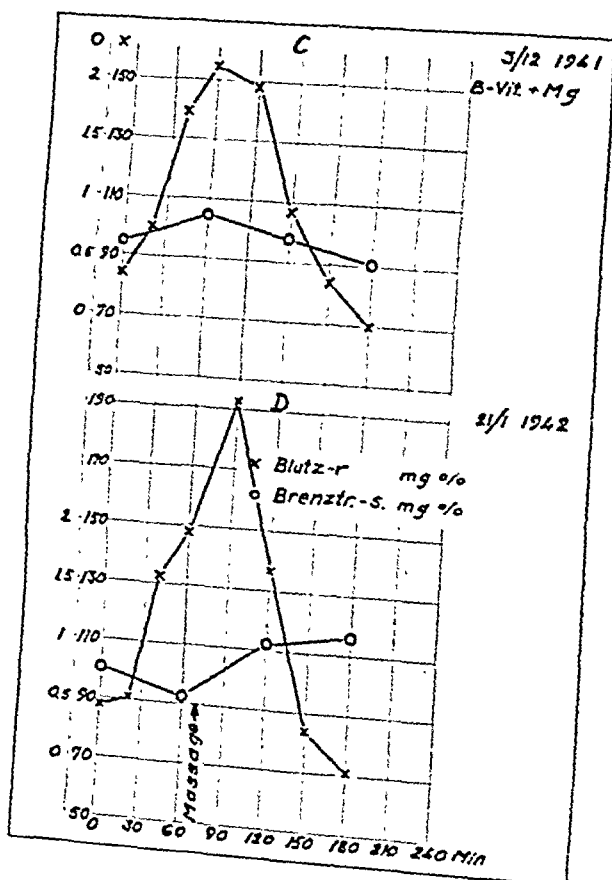
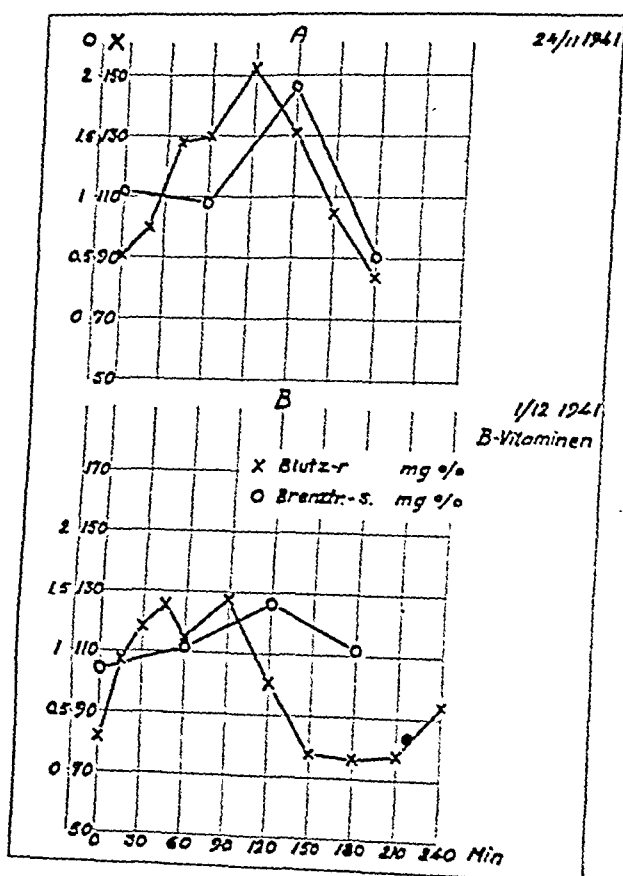


Fig. 1.



The explanation of the relationship between these two syndromes is uncertain. The treatment of the vitamin B deficiency led promptly to an improvement in some of the signs of polyneuritis (paresis of the vocal cords, pains in the upper arms), but the paresis in the legs and the changes in reflexes remained about as long as is usual in polyneuritis. It is possible that the very long period of regeneration for nerve fibers — 1 mm daily — concealed a real link between the vitamin B deficiency and the paresis. In other words, perhaps the polyneuritis really was caused by a lack of vitamin B, and the administration of vitamin B cured the disease. At present, however, the only justifiable conclusion is that the avitaminosis and the polyneuritis were subsidiary results of the intestinal disease. However, in our opinion, the causal chain is as follows: intestinal disease — vitamin deficiency — polyneuritis. Nor can one exclude the possibility of a vicious circle with intestinal atony due to vitamin B deficiency.

No. 2. E. D. S. 42-year old shop assistant treated at the Neurologic Department from February 26 to March 15, 1941 (Record No. 204/41) under the diagnosis, myelopathy and achylia, and from December 19, 1941, to January 31, 1942 (Record No. 1108/41.)

*Family History:* The patient's father died of cerebral hemorrhage. Of her brothers and sisters one died of gastric ulcer, one of diabetes and a third probably of cerebral tumor.

*Earlier Diseases:* In 1917 the patient had poliomyelitis with paralysis of the right arm and leg, which regressed during a period of two weeks but did not disappear entirely until after three years. There was no residual weakness in the two limbs. The right leg was slightly shorter than the left. Otherwise the patient had always been healthy. She had no dyspeptic symptoms and no glossitis. Menstruation has recently been somewhat irregular. There was no history of alcoholism, venereal disease or occupational injury.

*Present Disease: Phase I.* In the spring of 1940 the patient noticed that the gait was impaired. The hips began to be stiff and the right leg seemed weak. A few months later the left leg also became weaker than normal, the gait began to be swaying and unsteady, and the patient had difficulty in climbing stairs. At the same time she began to have cramps in the legs and creeping sensations in the lower portion of the back, the hips and down the legs. Occasionally she also had an icy sensation radiating to the toes. Gradually a slight sensation of weakness developed in the right arm.

When the patient was first observed at the Neurologic Department the following notes were made:

*Physical examination:* The patient was a small, slight woman with dark skin which appeared sun-tanned. The papillas of the tongue were somewhat

low. The nails were normal. There was a long, sighing, systolic murmur, most pronounced at the apex of the heart. The heart was not increased in breadth. Roentgen examination revealed nothing pathologic. The systolic blood pressure was 130, the diastolic 90. The peripheral vessels were normal. The blood and urine were normal. Fractioned histamine meal: No free hydrochloric acid. *Mental examination:* The patient's mood was somewhat labile. The primary mental functions were normal. The response to the praxis tests was somewhat clumsy. *Neurologic examination:* The cranial nerves were normal. The strength was normal in the arms, but was reduced in all the joints of the right leg and in the ankle of the left leg, which joint was weaker than the corresponding one in the right leg. The dynamometer registered 17 kilograms for both right and left hands. The right leg was atrophic. There was a moderate, fine tremor in the chin and arms, which increased on intention. The legs, particularly the right one, exhibited the same type of tremor after movement. The gait was stiff and the left foot dragged somewhat. The response to the finger-nose and knee-heel tests was normal. Surface and deep sensibility was normal. The pupillary reflexes were normal; the muscular reflexes in the arms were distinctly exaggerated and symmetrical; the quadriceps reflex was more pronounced in the left leg; the Achilles reflex was absent in the left leg; the muscular reflexes in the right leg were normal; the plantar reflex in the left leg was absent; and there was a slight Babinski reflex in the left leg. The spinal fluid was normal, as was the double puncture according to Lagergren.

The patient was treated with vitamin B and Hepaforte, but the only result was the disappearance of the creeping sensations. The condition remained stationary after discharge from the hospital, but the patient was able to keep on working.

*Phase II.* In the beginning of December, 1941, the patient began to sleep badly and to be increasingly tired. While setting the tea table on December 17 she suddenly felt «as if everything was going to disappear.» She placed the cups beside the saucers and raised the sugar basin to her lips instead of the cup. She could not make her way to her room nor find the key-hole. When she had been helped to her room she could not turn on the light or pull down the blind. She said she could not see the people about her, but could distinguish light and objects as usual. She mistook the physician for a policeman. She came out of the attack in about an hour and was completely oriented. Next, twitching began in the right arm, which flexed and trembled involuntarily. The patient could not raise a cup to her lips due to the trembling. The condition remained unchanged for 24 hours.

The patient had taken no medicine or headache powders nor had she used any abortifacient.

The patient was re-admitted to the Neurologic Department for observation one and a half days after the attack began. *Physical examination:* The general condition was satisfactory, but the skin was still brownish with

no symmetrical rings of pigment or chloasma-like changes. The papillae of the tongue were somewhat atrophic. The lungs and heart were as before. The blood was normal. The sedimentation rate was 4 mm after one hour. The Ehrlich and Schlesinger tests of the urine gave positive results. Consequently, a series of tests were made of the hepatic function. The Meulengracht icteric index remained constant at 1:7 to 8; serum bilirubin according to Hijmans van den Bergh, 2.4 mg per cent; citric acid, 13.7 per milliliter of whole blood; phosphatase test (Buch and Buch) 8 E; galactose tolerance according to Bauer, excretion of 5 gm; hippuric acid test according to Quick, excretion as benzoic acid, 1.99 gm. General roentgenograms of the abdomen showed uncertain enlargement of the liver. Finally, the investigation was supplemented by a fractioned histamine meal which showed no free hydrochloric acid. —

*Mental examination:* The patient was quite clear and orientated. The primary mental functions were normal, except for the concentration and mental arithmetic tests, which were done imperfectly. The patient was restless and easily upset. There was no suggestion of aphasia or apraxia.

*Neurologic examination:* The condition was the same as at the previous examination. The spinal fluid was normal.

The patient was now given vitamin B (1 Beveran tablet three times daily) for two weeks, after which corresponding preparations were given parenterally (2 MI twice daily). An estimation of the pyruvic acid concentration for the purpose of orientation gave an elevated value (1.6 mg per cent). A glucose tolerance test and a pyruvic acid determination made at the same time gave elevated pyruvic acid values, which reached a maximum of 1.7 mg per cent after 130 minutes (fig. 2a). It should be emphasized that the elevated pyruvic acid values were secured despite the fact that the patient had been receiving vitamin B for several weeks. The liver injury should perhaps be borne in mind in this connection, since cases of hepatitis are often found to exhibit an increase in the pyruvic acid content of the blood (Hammarsten and Stähle), which is not affected by the administration of vitamin B, but is affected by insulin. Seven days later the same tests were made again. The fasting value for pyruvic acid was now 0.96 mg per cent and the maximum was reached with 1.3 mg per cent after 120 minutes (fig. 2b). As in the foregoing case, magnesium salt was now given in addition to vitamin B, and nine days later another tolerance test was made. All the pyruvic acid values were lower than 1 mg per cent, with the exception of the fasting value, 1.1 mg per cent (fig. 2c).

During the period of observation the clinical picture remained stationary and only the general condition improved. Six months later we were informed that the patient had suddenly had another short period of confusion for which she was admitted to Beckomberga Mental Hospital.

*Summary and discussion:* A 42-year old woman had poliomyelitis at the age of 16 with no after-effects. For two years before admission the gait was impaired and there was paresthesia in both legs.

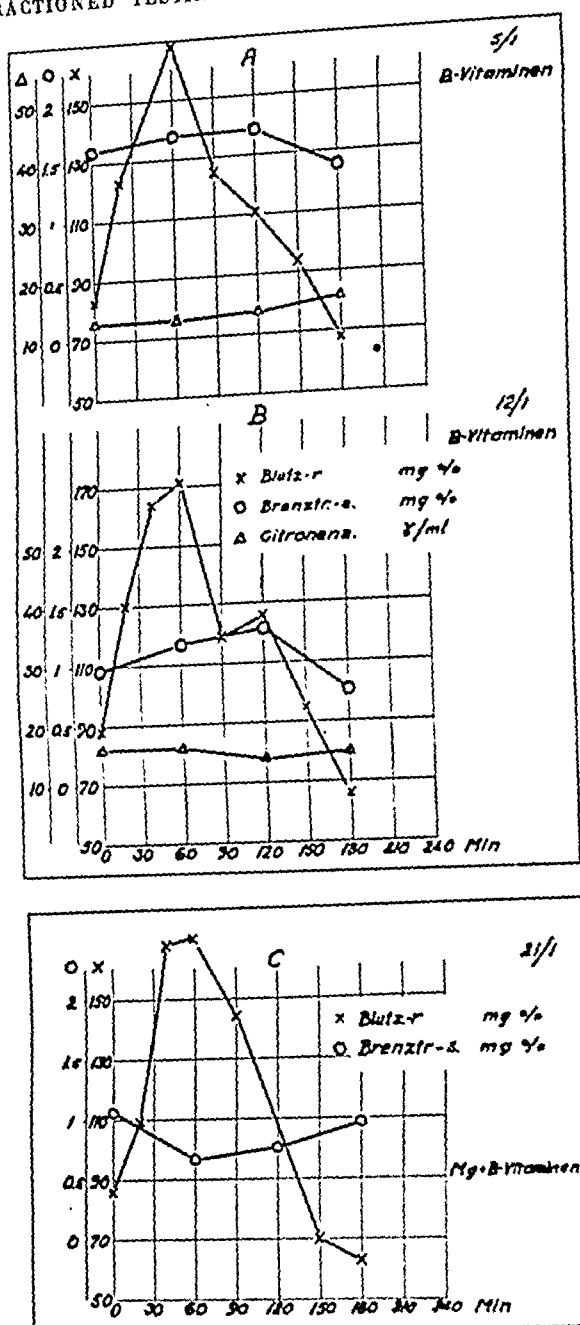


Fig. 2.

Upon observation at the Neurologic Department she was found to have a histamine-refractory achylia and myelopathy. Her mood was also somewhat labile. The signs of the myelopathy consisted of a mild spastic paraparesis and exaggerated muscular reflexes. There were no signs from the pyramidal tract, however. The paresthesias disappeared with treatment with vitamin B. Nine months later the

patient had a brief period of confusion, followed by a day of twitching and tremor in the right arm. Observation 36 hours later at the Neurologic Department revealed increased fatigability with mild impairment of the primary mental functions, unchanged myelopathy and cirrhosis of the liver. Fractioned functional testing of the carbohydrate metabolism disclosed elevated pyruvic acid values. This sign improved after prolonged treatment with vitamin B, but did not disappear until after the addition of magnesium salt. Six months later there was a short recurrence of the confusion.

As in the foregoing case, this patient also had digestive disturbances as well as cirrhosis of the liver. The combination, achylia, cirrhosis and myelopathy, is common. It cannot be stated definitely that the connecting link between these syndromes is to be found in the carbohydrate metabolism, although it seems probable. In this case, too, the treatment with vitamin B and magnesium acted on the disturbance in sensibility, but had no effect on the organic neurologic changes (paresis, changed reflexes). The latter fact does not necessarily disprove a connection with vitamin B deficiency. Strictly speaking, however, one can for the present only note the presence of an achylia and cirrhosis, as well as a vitamin B deficiency and an organic neurologic disturbance.

The short attacks of confusion are interesting. They have long been observed in connection with various forms of myelopathy. Episodic psychoses of this kind in connection with hyperchromic anemia and achylanemia have been described by Marcus, Bringel, Scheid, Cleckley, Sydenstricker, and others, while Joliffe et al. observed them in cases of vitamin B deficiency. The latter workers considered they had found a form of encephalopathy caused by nicotinic acid deficiency and which, in addition to delirium, is characterized by extrapyramidal signs. The hyperkinetic symptoms which the patient in question exhibited in one arm in the form of twitching and tremor, increasing on intention, are suggestive of this type of process. This possibility was unfortunately not taken into consideration and the excretion of nicotinic acid was not studied. — The whole disease picture is still very obscure and it remains to be seen how the case develops. The combination, cirrhosis of the liver, mental symptoms and intention tremor, may possibly constitute the first manifestations of an atypical hepatolenticular degeneration.

As soon as the patient began to receive vitamin B her headache disappeared and she felt generally better. From then on she remained free from symptoms as long as she continued the medication.

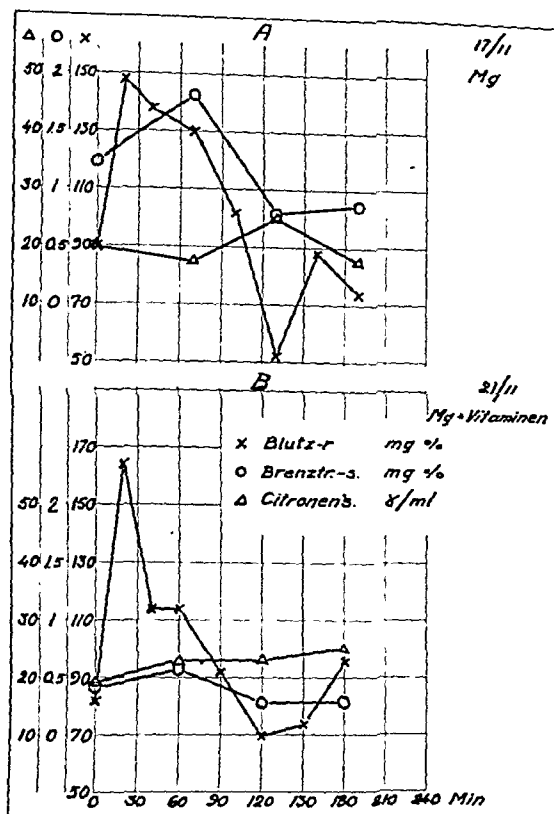


Fig. 3.

**Summary and discussion:** A woman of 45 years had periodic hemicrania-like headache following influenza in 1920, which in recent years took on the character of neuralgic pain in the right half of the face. The patient had a recurrent colitis with signs of impaired absorption of vitamin C of many years' standing. Physical and neurologic examinations revealed nothing pathologic. With magnecyl as the only medication, a glucose and pyruvic acid tolerance test was made, yielding elevated pyruvic acid values. A further examination was made after aneurin had been administered for four days, during which the headache disappeared. The pyruvic acid standard was now normal. No definite changes in the blood sugar were observed.

The part played by vitamin B deficiency is unclear in this case also. The severe infection in 1920, which gave nervous symptoms, as well as the heredity of glaucoma, suggests that a deficiency of vitamin B was not the cause of the hemicrania, which at first was typical. A review of the literature discloses only one extensive work (Palmer) in which aneurin is stated to be valuable in the treatment of migraine. Palmer based his claims on 50 »severe» cases, 23 of which became free from symptoms, and 14 improved. The really rapid effect of the aneurin treatment indicates a connection between the neuralgia-like pains and the vitamin B deficiency. It may be that the avitaminosis, with its depressing effect on the organism caused by impaired resorption, constituted an inciting factor in the appearance of the pain.

To summarize, it may be said that the method of fractioned glucose tolerance and pyruvic acid determination evolved by Hammarsten provides a means of disclosing disturbances in the carbohydrate metabolism manifested by an abnormal accumulation of pyruvic acid. Disturbances of this kind were present in all three cases of neurologic disease described herein. Treatment with vitamin B had a favourable effect on the carbohydrate metabolism, but normal pyruvic acid values were not secured until magnesium salts were administered. The connection between the vitamin B deficiency and the neurologic disturbances in these cases is not entirely clear. Treatment with vitamin B has a good effect on pain, paresthesia and mild paresis like the paralysis of the vocal cords in the first case. The more serious changes, like the paresis in the legs and the reflex changes, regress in the same way now as they did when the treatment with vitamin B was still unknown. Despite this, a causal relationship between the vitamin B deficiency and the nervous diseases in three foregoing cases is not improbable.

### Summary.

The carbohydrate metabolism was investigated in three cases of neurologic diseases by means of repeated glucose tolerance tests and pyruvic acid determinations. The method of investigation has been described by Hammarsten. Case 1 was an example of polyneuritis caused by ileus. The patient in Case 2 had a myelopathy

with attacks of confusion and achylia and cirrhosis of the liver. In Case 3 the patient was a woman with recurrent colitis who suffered from neuralgic pains in the face. In all three cases the pyruvic acid values were elevated. The blood sugar curves exhibited insignificant deviations. The treatment with vitamin B reduced the pyruvic acid values, but normal conditions were not restored until magnesium was given. The relation between the vitamin B deficiency and the neurologic diseases is discussed.

### Zusammenfassung.

An drei Patienten mit neurologischen Krankheiten wurde der Kohlenhydratstoffwechsel untersucht, mittels wiederholten Glykosebelastungen und Bestimmungen der Brenztraubensäure. Das Untersuchungsschema wurde von Hammarsten angegeben. Fall 1 war eine durch Ileus verursachte Polyneuritis. Fall II Myelopathie mit akuter Verwirrtheit sowie Achylie und Lebercirrhose. Fall III neuralgische Gesichtsschmerzen bei einer Frau mit recidivierender Colitis. In allen 3 Fällen war die Brenztraubensäure erhöht. Die Blutsuckerkurven zeigten geringe Abweichungen. B-vitaminbehandlung senkt die Brenztraubensäurewerte, vollständig normale Werte erhält man jedoch erst nach Magnesiumzugabe. Die Relation zwischen B-Avitaminosen und neurologischen Krankheiten wird diskutiert.

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From the Copenhagen University Institute of General Pathology (Chief: Professor K. A. Jensen, M. D.). The Kommunehospital, Second Department (Chief: Professor H. J. Bing, M. D.) and Seventh Department (Chief: Tage Bjerling, M. D.).

## Studies on twenty-four hour urea clearance.\*

By

METTE HERTZ.

(Submitted for publication October 28, 1942).

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### *Introduction.*

Of the various renal function tests those now chiefly employed in the clinic are the concentration test and the urea clearance test. The concentration test is often employed with Addis's modification and shows to what extent the kidneys are capable of concentrating the urine, so that it is mainly a test of the tubulus function. Urea clearance on the other hand in most cases is purely a glomerular test, as Bjerling and others have clearly demonstrated. This parallelism between urea clearance and filtration will be found as long as the urine is not concentrated beyond a certain limit, one that lies at a concentration index of 75 (Bing and Bjerling). If the urine is concentrated beyond this point, more urea will pass back through the tubules together with the increased reabsorption of water.

For the purpose of making comparisons from case to case and from time to time in the same patient, Eggert Møller, McIntosh and Van Slyke introduced a calculation of the standard clearance, by which it is possible to correct the values of the clearance of concentrated urines. In other words, they introduced a correction that eliminates the variation in the tubular phase of the excretion,

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\* Aided by a grant from P. A. Brandts legacy.

so that in all cases of urea clearance one seeks for information merely as to the glomerular function: the filtration.

The urine concentration test and the urea clearance test are both performed in the forenoon within a period of few hours, thirsting and after ingesting water respectively, i. e. under standard conditions that differ from the conditions under which the patient otherwise lives. We have no function test to show the functioning of the kidneys throughout the twenty-four hours.

It has therefore been the purpose of this work to endeavour to establish a twenty-four hour renal function test; urea would seem to be suitable, as it is filtered out through the glomeruli and in part passes back through the tubuli, so that the excretion of urea will be affected by a lesion of both glomeruli and tubuli. In addition, urea determination is an easy process and has already been adopted in many hospitals. Finally, by determining the twenty-four hour urea clearance it will be possible to reduce the diuresis error which often compromises the one-hour clearance.

### *Blood Urea's Twenty-four Hour Fluctuations.*

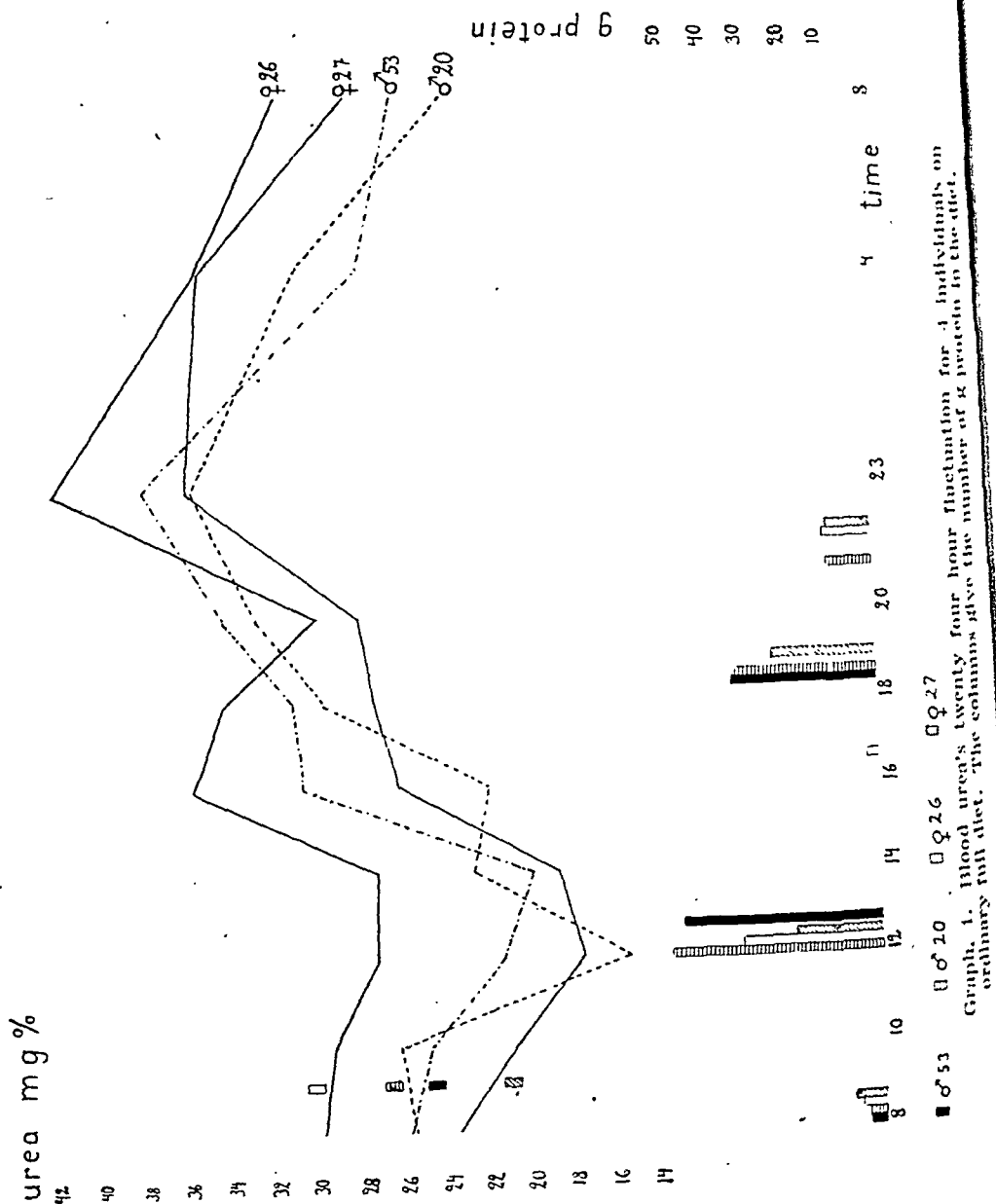
If the function test is to be extended over a whole day, it is a condition that the blood urea is more or less constant during that time.

The literature contains a number of investigations on the twenty-four hour fluctuations of blood urea, but the results differ a great deal. In 1915 Bang observed little or no increase of blood urea after an ordinary protein-rich meal, and a heavy increase after the ingestion of large quantities of meat (750 and 900 g). MacKay & MacKay watched the twenty-four hour fluctuations of blood urea in six experimental individuals who received an ordinary diet (1.1 g protein per kg per day); they observed a tendency to increase in the course of the day, strongest after the most protein-rich meal, and a fall at night. The fluctuations were not especially marked, the greatest variation in the course of one day being from 20 to 30 mg % urea.

Wittermans observed very heavy fluctuations of the blood urea of normal individuals on ordinary diet; during inanition the variations were even more pronounced (over 100 per cent.). Similar ob-

*Own Investigations.*

Blood urea samples were taken from four healthy individuals living on an ordinary full diet and having light manual work. In the course of 24 hours blood samples were taken every two hours from 8 am. to 8 pm and at 11 pm., 4 am. and 8 am. next day. Graph 1



Graph 1. Blood urea's twenty four hour fluctuation for 4 individuals on ordinary full diet. The columns give the number of g protein in the diet.

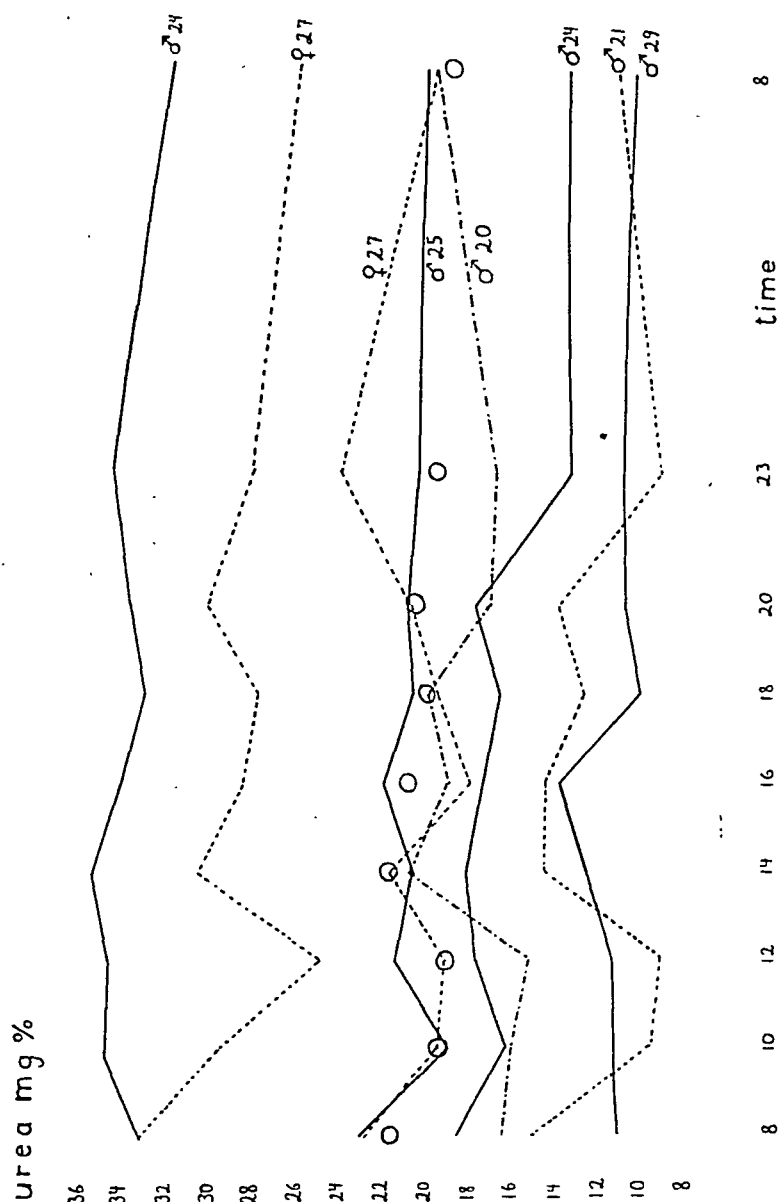
shows the blood urea fluctuations and the amount of protein in the diet. A feature common to all the curves is a fall during the forenoon and a rise two to four hours after lunch, whereafter, subsequent to a slight fall or a slight rise, it again rises steeply and reaches the maximum at 11 pm. Next morning at 8 o'clock the blood urea value is practically just as high as at 8 am. the day before (greatest difference 23.5—28.0 mg %). The fluctuations in the blood urea are rather marked, the greatest oscillations over and under the average value being about 30 per cent. The highest and lowest values for blood urea lie respectively 40—53 per cent. over and 10—10 per cent. under the initial value.

Table 1.

| Age, sex | Aver. urea mg% 24 hrs. | Max. in mg% | Min. in mg% | Max. var. over aver. mg% urea | Max. var. under aver. mg% urea | Max. var. over % | Max. var. under % | G. protein per 24 hrs | G. protein per kg |
|----------|------------------------|-------------|-------------|-------------------------------|--------------------------------|------------------|-------------------|-----------------------|-------------------|
| 26 ♀     | 33.1                   | 42.1        | 27.2        | 9.0                           | 5.9                            | 27               | 18                | 83.7                  | 1.57              |
| 27 ♀     | 27.7                   | 36.0        | 17.5        | 8.3                           | 10.2                           | 30               | 37                | 69.0                  | 1.24              |
| 20 ♂     | 27.5                   | 35.7        | 15.4        | 8.2                           | 12.1                           | 30               | 44                | 106.5                 | 1.43              |
| 53 ♂     | 28.7                   | 38.0        | 19.9        | 9.3                           | 8.8                            | 32               | 31                | 91.4                  | 1.20              |
| Average: | 29.3                   |             |             | 8.7                           | 9.3                            | 30               | 33                |                       |                   |

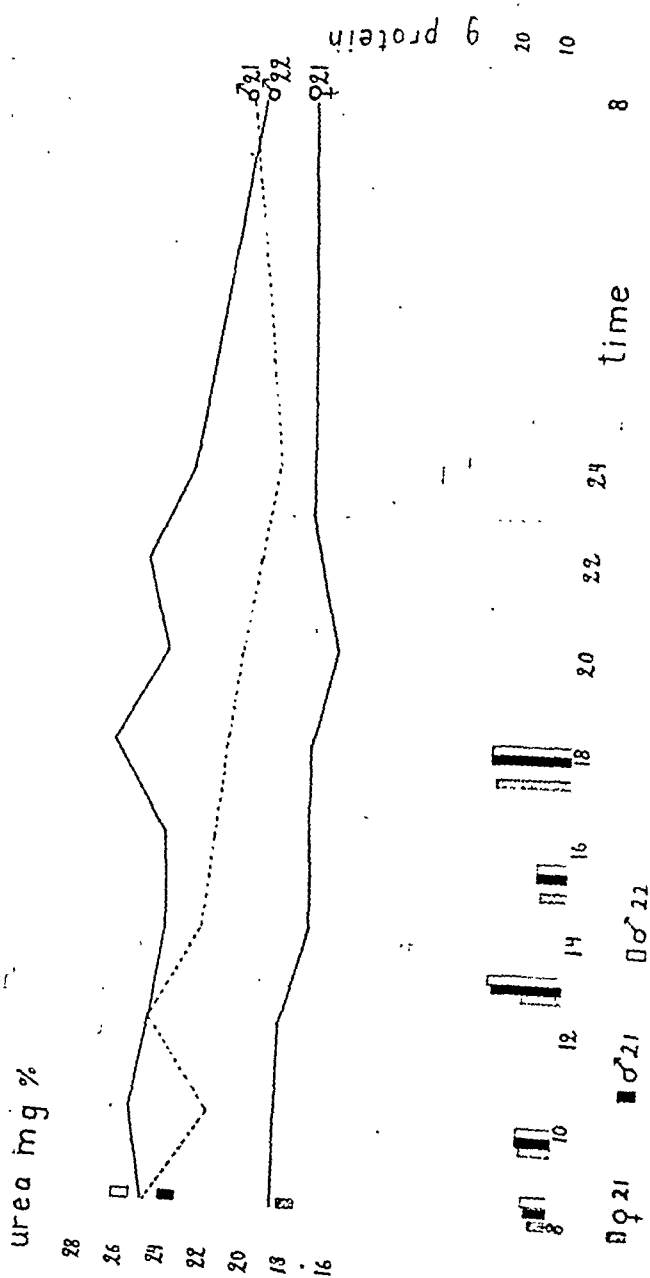
The average value of blood urea is calculated as the mean of the values at 8 am., 10 am., 12 am., etc. up to 8 pm., the values at 10 pm., 24 pm. and 6 am. being determined by interpolation.

In order to ascertain whether the fluctuations are due to diet or to other factors, eight individuals (6 males and 2 females) not confined to bed were tested; they had received a diet less rich in proteins (in all 38—62 g) divided over three meals. It will be seen from Graph 2 that the blood urea varies less on the protein-poor diet. The average curve falls during the forenoon and rises 1 ½ to 2 hours after dinner, whereafter there is a slight fall until next morning. On the whole the curve falls during the twenty-four hours. The oscillations in relation to the average value are about half of those recorded for the first diet with more proteins, as will be seen from the following table:



Graph 2. Blood urea's twenty four hour fluctuation for 8 individuals on protein-poor diet. Average values for the 8 individuals indicated by circles.

Next, tests were made on two males and one female who had received a similar diet (43—56 g protein per day), but distributed more evenly over the day, this diet, used in the following experiments, will be described later. They had eaten this food for two days; and the blood urea was tested ten times in the course of the second day, the individuals being confined to bed. Graph 3 shows



Graph 3. Blood urea's twenty four hour fluctuation for 3 individuals on protein-poor diet. The columns give the number of g protein in the diet.

the fluctuations of the blood urea and the protein content of the food. Here the oscillations in relation to the average values are somewhat less than with the previous meal distribution; the greatest oscillation over the average is 12, 14 and 15 per cent. respectively, and under the average 11, 9 and 9 per cent. The fluctuations being so small, I tested the relation of the average value of all ten deter-

Table 2.

| Age, sex | g. Protein | g Protein per kg | Average urea mg % | Max. urea mg % | Min. urea mg % | Max. var. above average mg % | Max. var. under average mg % | Max. var. above average % | Max. var. under average % |
|----------|------------|------------------|-------------------|----------------|----------------|------------------------------|------------------------------|---------------------------|---------------------------|
| 27 ♀     | 41.3       | 0.73             | 20.8              | 23.8           | 17.9           | 3.0                          | 2.9                          | 14                        | 14                        |
| 27 ♀     | 39.9       | 0.73             | 28.2              | 33.3           | 24.9           | 4.9                          | 3.9                          | 17                        | 14                        |
| 21 ♂     | 40.5       | 0.60             | 11.2              | 15.1           | 8.6            | 3.9                          | 2.6                          | 35                        | 23                        |
| 20 ♂     | 57.8       | 0.97             | 17.8              | 20.9           | 15.2           | 3.1                          | 2.6                          | 17                        | 15                        |
| 24 ♂     | 62.5       | 0.89             | 15.5              | 18.5           | 13.0           | 3.0                          | 2.6                          | 19                        | 16                        |
| 24 ♂     | 59.1       | 0.78             | 33.6              | 35.4           | 31.5           | 1.8                          | 2.1                          | 5                         | 6                         |
| 25 ♂     | 52.0       | 0.72             | 20.6              | 23.4           | 18.9           | 2.8                          | 1.7                          | 14                        | 8                         |
| 29 ♂     | 38.0       | 0.51             | 10.8              | 13.7           | 9.7            | 2.9                          | 1.1                          | 19                        | 10                        |

The average value of blood urea is calculated as the mean of the values at 8 am., 10 am., 12 am. etc. up to 8 pm., the values at 10 pm., 24 pm. and 6 am. being determined by interpolation.

minations to an average of fewer determinations; in this case I employed the average blood urea values at 8 am., 2 pm., 8 pm., 2 am. (interpolated value) and 8 am. The result will be seen in table 3.

As the average blood urea value in twenty-four hours determined on four values differs only little from the average value of ten, I made tests of the blood urea of 31 hospital patients with healthy kidneys, taking four blood samples in the twenty-four hours. For these patients I compiled a menu containing 50 g protein per day, i. e. about three-fifths of what is contained in the ordinary hospital diet; I endeavoured to make the diet satisfying, tasty and varied.

Table 3.

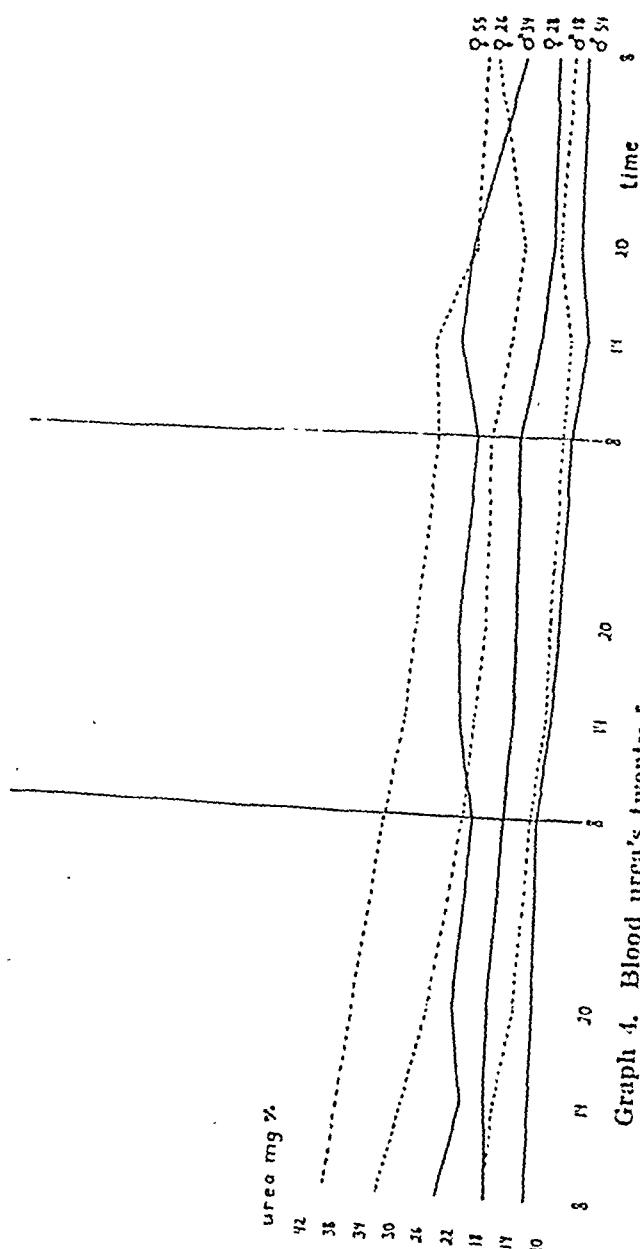
| Sex, age | G. protein per 24 hrs | G. protein per kg | Average of 10 determ. mg % urea | Average of 4 determ. mg % urea | Deviation mg % urea | Deviation % |
|----------|-----------------------|-------------------|---------------------------------|--------------------------------|---------------------|-------------|
| 22 ♂     | 56.1                  | 0.81              | 24.5                            | 24.0                           | 0.5                 | 2.0         |
| 21 ♂     | 54.6                  | 0.72              | 22.1                            | 22.8                           | 0.7                 | 3.2         |
| 21 ♀     | 43.6                  | 0.69              | 18.5                            | 18.1                           | 0.4                 | 1.6         |

Its composition was as follows:

|  |               |
|--|---------------|
| 8 am. Slice of white bread, slice of bolted rye bread, butter, tea | 4.7 g protein |
| 9.30 am. 250 g oatmeal porridge, 100 ccm <sup>3</sup> milk         | 8.6 g         |
| 1 pm. Dinner   |               |
| 3.30 pm. 200 ccm <sup>3</sup> cocoa substitute or milk             | 6.6 g         |
| 5.15 pm. Supper:   |               |

Half-slice ryebread with tomato, carrot etc.

|   |   |   |                                    |             |
|---|---|---|------------------------------------|-------------|
| " | " | " | smoked sausage or<br>collared meat |             |
| " | " | " | liver-paste                        | .... 12.7 g |
| " | " | " | cheese                             |             |



Graph 4. Blood urea's twenty four hour fluctuation for individuals on protein-poor diet. The scale is the half of that used in the foregoing curves.



| Sex,<br>age. | Days on<br>protein-<br>poor diet. | Average<br>blood-urea<br>mg % | Maxi-<br>mum | Mini-<br>mum | Max. var.<br>above<br>average. | Max. var.<br>under-<br>average. | Max.<br>var.<br>above<br>% | Max.<br>var.<br>under<br>% |
|--------------|-----------------------------------|-------------------------------|--------------|--------------|--------------------------------|---------------------------------|----------------------------|----------------------------|
| 41 ♂         | 1                                 | 22.6                          | 23.8         | 20.7         | 1.2                            | 1.9                             | 5                          | 8                          |
|              | 2                                 | 21.7                          | 23.4         | 20.8         | 1.7                            | 0.9                             | 8                          | 4                          |
| 27 ♀         | 1                                 | 23.6                          | 26.3         | 22.2         | 2.7                            | 1.4                             | 11                         | 6                          |
|              | 2                                 | 20.7                          | 23.1         | 17.5         | 2.4                            | 3.2                             | 12                         | 15                         |
| 18 ♀         | 2                                 | 20.9                          | 23.8         | 18.6         | 2.9                            | 2.3                             | 13                         | 11                         |
|              | 3                                 | 19.6                          | 23.8         | 17.1         | 4.2                            | 2.5                             | 21                         | 13                         |
| 30 ♀         | 1                                 | 23.4                          | 24.0         | 21.9         | 0.6                            | 1.5                             | 3                          | 0                          |
|              | 2                                 | 19.6                          | 23.9         | 16.1         | 4.3                            | 3.5                             | 22                         | 18                         |
|              | 3                                 | 18.1                          | 20.5         | 16.1         | 2.4                            | 2.0                             | 13                         | 11                         |
| 56 ♂         | 1                                 | 31.7                          | 34.1         | 30.2         | 2.4                            | 1.5                             | 8                          | 5                          |
|              | 2                                 | 32.8                          | 35.4         | 31.0         | 2.6                            | 1.8                             | 8                          | 5                          |
| 18 ♀         | 1                                 | 20.5                          | 24.6         | 17.7         | 4.1                            | 2.8                             | 20                         | 14                         |
|              | 2                                 | 18.3                          | 20.1         | 16.1         | 1.8                            | 2.2                             | 10                         | 12                         |
| 49 ♂         | 1                                 | 21.7                          | 22.8         | 19.7         | 1.1                            | 2.0                             | 5                          | 9                          |
|              | 2                                 | 21.7                          | 22.8         | 19.7         | 1.1                            | 2.0                             | 5                          | 9                          |
| 27 ♂         | 1                                 | 24.7                          | 26.8         | 23.2         | 2.1                            | 1.5                             | 9                          | 6                          |
|              | 2                                 | 22.9                          | 25.2         | 19.3         | 2.3                            | 3.6                             | 10                         | 16                         |
| 18 ♀         | 1                                 | 20.0                          | 21.0         | 18.5         | 1.0                            | 1.5                             | 5                          | 8                          |
|              | 2                                 | 21.8                          | 23.1         | 20.5         | 1.3                            | 1.3                             | 6                          | 6                          |
| 41 ♂         | 1                                 | 32.5                          | 33.7         | 30.3         | 1.2                            | 2.2                             | 4                          | 7                          |
|              | 2                                 | 29.8                          | 33.7         | 27.0         | 3.9                            | 2.8                             | 13                         | 9                          |
|              | 3                                 | 23.8                          | 27.0         | 22.3         | 3.2                            | 1.5                             | 13                         | 6                          |
| 54 ♂         | 1                                 | 22.3                          | 24.9         | 19.1         | 2.6                            | 3.2                             | 12                         | 14                         |
|              | 3                                 | 21.8                          | 23.7         | 19.9         | 1.9                            | 1.9                             | 9                          | 9                          |
| average      |                                   |                               |              |              |                                |                                 | 10.0                       | 9.5                        |

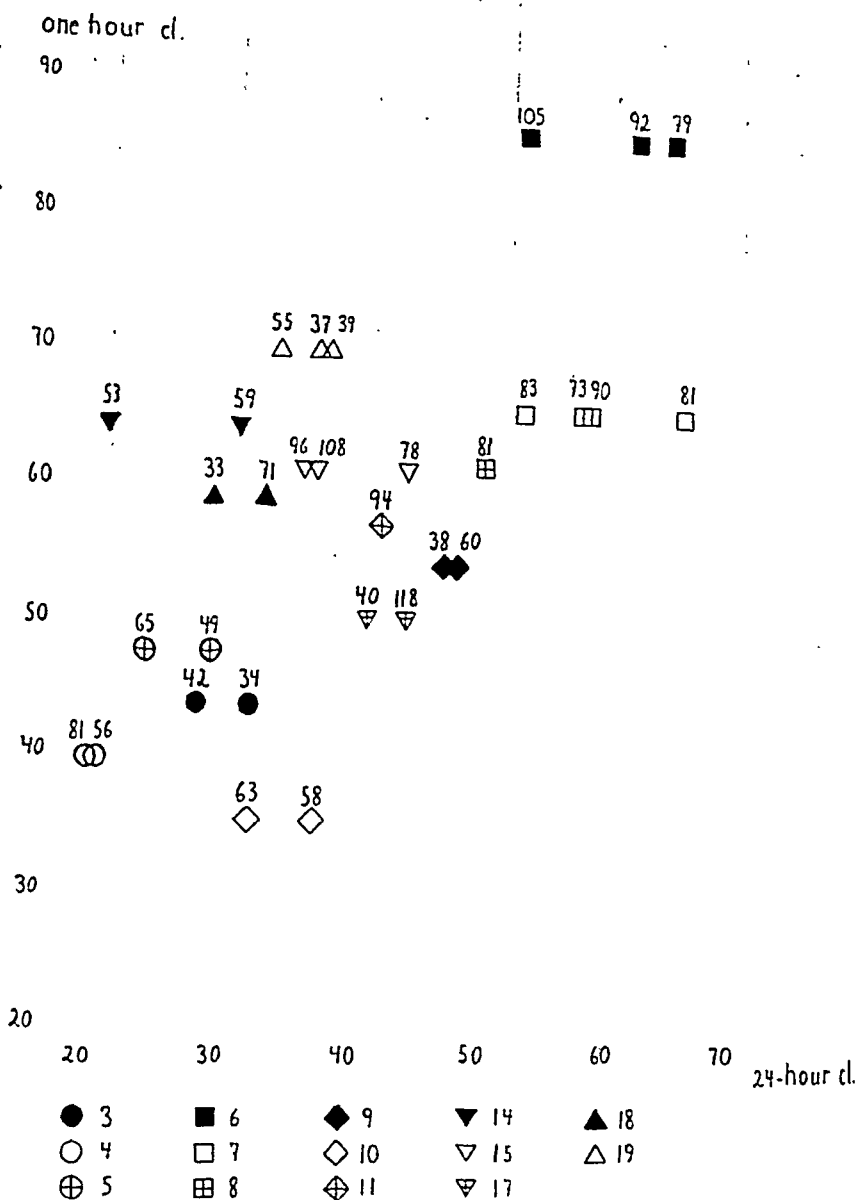
Dinners were: Pea-soup with cabbage, fried vegetables with forcemeat = 18.0 g protein. — Fried tomato with potato-rissole, stewed prunes with cream = 17.2 g protein. — Corn-flour stirabout with fruit juice, celery cutlet with tomato sauce = 16.8 g protein. — Vegetables and butter, rice pudding with apples = 17.7 protein.

The patients received this diet for one to three days, and at the same time the blood urea was tested at 8 am., 2 pm., 8 pm. and 8 am. Some typical examples of the blood-urea curves will be seen in Graph 4. Table 4 shows how much the blood-urea values fluctuate in proportion to the average values in twenty-four hours.

It would be natural to assume that the average blood urea may be determinable from still fewer tests than these four. Table 5 gives an average of the two values found at 8 am. on two successive mornings compared with the average of all tests made during the twenty-four hours. The greatest deviation is 2 mg %, correspond-

| Sex Age. | Days on protein-poor diet. | No. determinations in 24 hours. | Average of all determinations mg % | Average 8am + 8am mg % urea. | Difference mg % urea. | Difference % |
|----------|----------------------------|---------------------------------|------------------------------------|------------------------------|-----------------------|--------------|
| 62 ♀     | 2                          | 4                               | 23.2                               | 22.5                         | 0.7                   | 3            |
|          | 3                          | 4                               | 20.7                               | 20.6                         | 0.1                   | 0            |
| 58 ♀     | 2                          | 4                               | 26.0                               | 25.6                         | 0.4                   | 2            |
|          | 3                          | 4                               | 24.1                               | 25.4                         | 1.3                   | 5            |
| 34 ♂     | 1                          | 4                               | 22.1                               | 22.5                         | 0.4                   | 2            |
|          | 2                          | 4                               | 23.0                               | 22.0                         | 1.0                   | 4            |
|          | 3                          | 4                               | 23.6                               | 22.5                         | 1.1                   | 5            |
| 32 ♂     | 1                          | 4                               | 17.7                               | 18.4                         | 0.7                   | 4            |
|          | 2                          | 4                               | 22.5                               | 21.1                         | 1.4                   | 6            |
|          | 3                          | 4                               | 21.0                               | 21.5                         | 0.5                   | 2            |
| 32 ♀     | 2                          | 4                               | 15.3                               | 14.2                         | 1.1                   | 7            |
|          | 3                          | 4                               | 16.0                               | 15.7                         | 0.3                   | 3            |
| 28 ♀     | 1                          | 4                               | 17.6                               | 17.2                         | 0.4                   | 2            |
|          | 3                          | 4                               | 14.5                               | 15.4                         | 0.9                   | 6            |
| 41 ♂     | 1                          | 4                               | 22.6                               | 22.1                         | 0.5                   | 2            |
|          | 2                          | 4                               | 21.7                               | 22.1                         | 0.4                   | 2            |
| 27 ♀     | 1                          | 4                               | 23.6                               | 23.1                         | 0.5                   | 2            |
|          | 2                          | 4                               | 20.7                               | 19.9                         | 0.8                   | 4            |
| 18 ♀     | 2                          | 4                               | 20.9                               | 21.8                         | 0.9                   | 4            |
|          | 3                          | 4                               | 19.6                               | 21.0                         | 1.4                   | 7            |
| 30 ♀     | 1                          | 4                               | 23.4                               | 24.0                         | 0.6                   | 3            |
|          | 2                          | 4                               | 19.6                               | 20.0                         | 0.4                   | 2            |
|          | 3                          | 4                               | 18.1                               | 18.3                         | 0.2                   | 1            |
| 28 ♀     | 1                          | 4                               | 29.5                               | 29.7                         | 0.2                   | 1            |
| 56 ♂     | 1                          | 4                               | 31.7                               | 30.8                         | 0.9                   | 3            |
|          | 2                          | 4                               | 32.8                               | 31.9                         | 0.9                   | 3            |
| 18 ♀     | 1                          | 4                               | 20.5                               | 18.7                         | 1.8                   | 9            |
|          | 2                          | 4                               | 18.3                               | 17.9                         | 0.4                   | 2            |
| 49 ♂     | 1                          | 4                               | 21.7                               | 21.9                         | 0.2                   | 1            |
|          | 2                          | 4                               | 21.7                               | 21.3                         | 0.4                   | 2            |
|          | 3                          | 4                               | 19.6                               | 19.2                         | 0.4                   | 2            |
| 27 ♂     | 1                          | 4                               | 24.7                               | 24.1                         | 0.6                   | 4            |
|          | 2                          | 4                               | 22.9                               | 21.3                         | 1.6                   | 7            |
| 18 ♀     | 1                          | 4                               | 20.0                               | 20.2                         | 0.2                   | 1            |
|          | 2                          | 4                               | 21.8                               | 22.1                         | 0.3                   | 1            |
| 41 ♂     | 1                          | 4                               | 32.5                               | 32.5                         | 0                     | 0            |
|          | 2                          | 4                               | 29.8                               | 30.4                         | 0.6                   | 2            |
|          | 3                          | 4                               | 23.8                               | 24.7                         | 0.9                   | 4            |
| 54 ♂     | 1                          | 4                               | 22.3                               | 23.4                         | 1.1                   | 5            |
|          | 2                          | 4                               | 21.8                               | 21.8                         | 0                     | 0            |
| average  |                            |                                 |                                    |                              |                       | 3.1 %        |

The first 8 individuals have got another meal distribution (3 meals) than the following, and because that they are not included in the calculation of average deviation and probable deviation.



ing to an error of 10 per cent. The average deviation for the 81 days is 3.1 per cent.

It will be seen from the table that 91 per cent. of the results from two tests differ no more than 6 per cent from the result of four or more tests. As the distribution of the deviation is fairly exponential, it may be said with great certainty that at least 82 per cent. ( $= 91$  per cent. less  $3 \times$  the standard deviation) of the two-test results have a deviation that is less than or equal to 6 per cent. of the average of the four-test results. The error will presumably be reduced by calculating the average of several twenty-four hour clearances.

With the diet described it is possible to bring about a relative stability in the blood urea, whereby the average value of the blood urea during the twenty-four hours can be judged by determining the value on two successive mornings. The diet has the advantage that it is easy to use in a hospital, as its only essential difference from the usual hospital diet lies in the midday meal.

#### *Twenty-four Hour Urea Clearance.*

Next I tested the twenty-four hour clearance of 22 patients (8 males and 14 females). The patients were confined to bed, except for one or two who were allowed up for a couple of hours during the day. They received the aforesaid diet containing about 50 g protein per day (34—53 g), or 0.47—1.1 g protein per kg per day. For the majority of these patients their blood urea was measured at 8 am., 2 pm., 8 pm. and 8 am next morning; for one or two it was measured only at 8 am. Diuresis was measured from 8 am. to 8 am.; the urine was kept in a cool place, covered over and with a few drops of toluol added. For the first five patients the urea in the urine was determined by the micro-method, otherwise by Van Slyke's and Cullen's method. Double analyses were made of the content of ammonia + urea and of ammonia; the urea was found as the result of subtracting these two values. For purpose of control an analysis of a urea solution of known concentration was made at the same time. In this solution 2 to 5 per cent. less urea was found than was expected. For each patient I made two or three twenty-four hour clearance determinations, and in addition an ordinary

Table

| Sex Age,<br>Diagnosis   | Days on pro-<br>tein-poor<br>diet | Blood-urea<br>average<br>mg % | 24 hour<br>diuresis        | Diuresis<br>per min.         | Urea in<br>urine<br>mg %     | NH <sub>3</sub> in<br>urine |
|---|-----------------------------------|-------------------------------|----------------------------|------------------------------|------------------------------|-----------------------------|
| 1 ♀ 61<br>deg. myocard.<br>bronchit. chr.                     | 2<br>3                            | 26.1<br>24.5                  | 1025<br>935                | 0.71<br>0.65                 | 1343<br>1241                 | 52<br>0                     |
| 2 ♀ 62<br>lumbago   | 2<br>3                            | 28.7<br>23.6                  | 393<br>584                 | 0.27<br>0.40                 | 1465<br>1576                 | 121<br>0                    |
| 3 ♀ 55<br>hypertensio,<br>hypertrofia cord. B. P.<br>200/110. | 2<br>3                            | 30.3<br>25.6                  | 1075<br>1175               | 0.75<br>0.82                 | 1280<br>878                  | 38<br>0                     |
| 4 ♀ 63<br>hypertensio,<br>adipositas,<br>B. P. 165/110        | 2<br>3                            | 23.2<br>20.7                  | 398<br>455                 | 0.25<br>0.35                 | 1873<br>1150                 | 0<br>0                      |
| 5 ♀ 58<br>hypertensio,<br>hypertrofia cordis.<br>B. P. 150/80 | 2<br>3                            | 26.0<br>24.1                  | 845<br>573                 | 0.59<br>0.40                 | 1274<br>1563                 | 79<br>0                     |
| 6 ♂ 34<br>seqv.<br>pneumonia                                  | 1<br>2<br>3                       | 22.1<br>23.0<br>23.6          | 964<br>1180<br>725         | 0.67<br>0.82<br>0.50         | 2037<br>1820<br>2472         | 81                          |
| 7 ♂ 32<br>polyarthr. ac.<br>mb. cord.<br>mitralis             | 1<br>2<br>3<br>1                  | 17.7<br>22.5<br>21.0<br>26.3  | 1215<br>1135<br>918<br>925 | 0.84<br>0.79<br>0.64<br>0.64 | 1380<br>1652<br>1900<br>2179 | 59<br>119                   |
| 8 ♀ 32<br>contusio fem.<br>dxt. seq. — e. l.                  | 1<br>2                            | (12.0)<br>15.3<br>16.0        | 480+<br>960<br>400+        | 0.36<br>0.62<br>0.27         | 1074<br>1238<br>1884         |                             |
| 9 ♀ 28<br>Polyarthr.<br>rheum. chr.                           | 1<br>2<br>3                       | 17.6<br>(17.0)<br>14.5        | 1809<br>925<br>1135        | 1.26<br>0.63<br>0.79         | 665.4<br>1198<br>876         | 60<br>144<br>98             |
| 10 ♂ 41<br>polyarthr.<br>acuta, — e. l.                       | 1<br>2                            | 22.6<br>21.7                  | 900<br>750                 | 0.63<br>0.52                 | 1322<br>1363                 | 93<br>135                   |
| 11 ♀ 27<br>Pleuritis<br>exsud. dx.                            | 1<br>2                            | 23.6<br>20.7                  | 625<br>420+                | 0.43<br>0.29                 | 2278<br>2139                 | 92<br>105                   |
| 12 ♀ 18<br>Polyarthritoidis<br>ac.                            | 1<br>2<br>3                       | (20.6)<br>20.9<br>19.6        | 562<br>520<br>760          | 0.39<br>0.37<br>0.53         | 1473<br>1369<br>1145         | 173<br>151<br>131           |
| 13 ♂ 56<br>Hypertrofia et deg.<br>myocard., lues vetus        | 1<br>2                            | 31.7<br>32.8                  | 800<br>830                 | 0.56<br>0.38                 | 1347<br>1460                 | 83<br>154                   |
| 14 ♀ 18<br>Hepatitis ac.                                      | 1<br>2                            | 20.5<br>18.3                  | 760<br>565                 | 0.53<br>0.39                 | 1203<br>965.8                | 66<br>74                    |
| 15 ♂ 49<br>Myosos pectorales,<br>neurastenia, — e. l.         | 1<br>2<br>3                       | 21.7<br>21.7<br>19.6          | 545<br>500<br>812          | 0.38<br>0.35<br>0.56         | 2037<br>2347<br>1535         | 83<br>156<br>127            |

| NH <sub>3</sub> in % of urea. | Urea conc. index. | g protein pr 24 hours | g protein per kg | ClSt average | ClSt 8 + 8 | Clmax average | Clmax 8 + 8 | 1-hour clearance | Urea conc. index for 1-hour clearance |
|-------------------------------|-------------------|-----------------------|------------------|--------------|------------|---------------|-------------|------------------|---------------------------------------|
| 4                             | 54                | 50.6                  |                  | 43           | 42         | 37            | 36          |                  |                                       |
| 0                             | 50                | 50.3                  |                  | 41           | 42         | 33            | 34          |                  |                                       |
| 9                             | 51                | 51.4                  | 0.86             | 27           | 27         | 14            | 14          |                  |                                       |
| 0                             | 68                | 50.6                  | 0.84             | 43           | 43         | 27            | 27          |                  |                                       |
| 2                             | 42                | 50.6                  | 0.89             | 37           | 36         | 32            | 31          | 44               |                                       |
| 0                             | 34                | 50.3                  | 0.89             | 31           | 31         | 28            | 28          | 43               |                                       |
| 0                             | 81                | 50.6                  | 0.64             | 40           | 42         | 20            | 21          | 40               |                                       |
| 0                             | 56                | 50.3                  | 0.63             | 33           | 33         | 20            | 20          | 39               |                                       |
| 7                             | 49                | 50.6                  | 0.80             | 38           | 38         | 20            | 29          | 50               |                                       |
| 0                             | 65                | 50.3                  | 0.79             | 39           | 41         | 24            | 26          | 45               |                                       |
| 4                             | 92                | 50.8                  | 0.73             | 75           | 74         | 62            | 61          | 94               | 23                                    |
|                               | 79                | 50.0                  | 0.72             | 72           | 75         | 65            | 68          | 79               | 19                                    |
|                               | 105               | 50.9                  | 0.73             | 74           | 78         | 53            | 55          |                  |                                       |
| 4                             | 78                | 50.8                  | 0.77             | 72           | 69         | 66            | 63          | 68               | 12                                    |
|                               | 73                | 50.0                  | 0.76             | 66           | 70         | 58            | 62          | 61               | 10                                    |
|                               | 90                | 49.7                  | 0.75             | 72           | 71         | 58            | 56          |                  |                                       |
| 5                             | 83                | 50.3                  | 0.76             | 66           | 67         | 53            | 54          |                  |                                       |
|                               | 90                | 50.8                  | 0.88             |              | 54+        |               | 33+         | 71               | 12                                    |
|                               | 81                | 50.0                  | 0.87             | 64           | 69         | 50            | 54          | 52               | 10                                    |
|                               | 118               | 49.7                  | 0.86             | 62+          | 63+        | 32+           | 33+         |                  |                                       |
| 9                             | 38                | 50.3                  | 0.87             | 42           | 43         | 47            | 49          | 54               | 8                                     |
| 12                            | 70                | 49.3                  | 0.86             |              | 56         |               | 44          |                  |                                       |
| 11                            | 60                | 49.7                  | 0.86             | 54           | 51         | 48            | 45          |                  |                                       |
| 7                             | 58                | 49.7                  | 0.86             | 46           | 47         | 37            | 37          | 35               | 5                                     |
| 10                            | 63                | 50.0                  | 0.85             | 45           | 45         | 32            | 32          |                  |                                       |
| 4                             | 94                | 46.0                  | 0.72             | 64           | 65         | 42            | 42          | 57               | 9                                     |
| 5                             | 103               | 47.9                  | 0.75             | 56+          | 58+        | 30+           | 31+         |                  |                                       |
| 12                            | 71                | 33.6                  | 0.47             |              | 45         |               | 28          |                  |                                       |
| 11                            | 66                | 42.2                  | 0.58             | 40           | 38         | 21            | 23          |                  |                                       |
| 11                            | 58                | 44.2                  | 0.61             | 42           | 40         | 31            | 29          |                  |                                       |
| 6                             | 42                | 50.6                  | 0.61             | 32           | 33         | 24            | 24          |                  |                                       |
| 11                            | 45                | 49.8                  | 0.60             | 34           | 35         | 26            | 26          |                  |                                       |
| 5                             | 59                | 50.6                  | 0.93             | 43           | 46         | 31            | 34          | 64               | 12                                    |
| 8                             | 53                | 48.4                  | 0.89             | 33           | 34         | 21            | 21          |                  |                                       |
| 4                             | 96                |                       |                  | 58           | 57         | 36            | 35          | 61               | 9                                     |
| 7                             | 108               | 47.9                  | 0.67             | 64           | 65         | 37            | 38          |                  |                                       |
| 8                             | 78                | 49.4                  | 0.67             | 59           | 60         | 44            | 45          |                  |                                       |

| Sex Age<br>Diagnosis | Days on pre-<br>teempoor<br>diet | Blood-urea<br>average<br>mg % | 24 hour<br>diuresis | Diuresis<br>per min. | Urea in<br>urine<br>mg % | NH <sub>3</sub> in<br>urine |
|----------------------|----------------------------------|-------------------------------|---------------------|----------------------|--------------------------|-----------------------------|
| 16 ♀ 33              | 1                                | (25.1)                        | 1550                | 1.08                 | 757                      | 65                          |
| Polyarthritis?       | 2                                | (20.9)                        | 1540                | 1.07                 | 733                      | 65                          |
| Adipositas, — c. l.  | 3                                | (19.0)                        | 1910                | 1.33                 | 377                      | 27                          |
| 17 ♂ 27              | 1                                | 24.7                          | 535                 | 0.37                 | 290.4                    | 91                          |
| Pneumonia dx.        | 2                                | 22.9                          | 1480                | 1.03                 | 911                      | 84                          |
| 18 ♀ 18              | 1                                | 20.0                          | 1270                | 0.88                 | 666                      | 105                         |
| Pneumonia            | 2                                | 21.8                          | 650                 | 0.45                 | 1556                     |                             |
| sin.                 | 3                                | (22.7)                        | 580                 | 0.40                 | 1188                     | 37                          |
| 19 ♂ 41              | 1                                | 32.5                          | 1430                | 0.99                 | 1217                     | 71                          |
| Pneumonia dx.        | 2                                | 29.8                          | 880                 | 0.61                 | 1650                     | 140                         |
| Ulcus ventr.         | 3                                | 23.8                          | 1385                | 0.96                 | 935                      | 93                          |
| 20 ♀ 42              | 1                                | (39.6)                        | 1000                | 0.69                 | 1757                     | 122                         |
| Ischias              | 2                                | (35.5)                        | 887                 | 0.62                 | 1537                     | 157                         |
|                      | 3                                | (33.3)                        | 910                 | 0.63                 | 1160                     |                             |
| 21 ♂ 54              | 1                                | 22.3                          | 1010                | 0.70                 | 990                      | 56                          |
| Cirrhosis            | 3                                | 21.8                          | 1515                | 1.05                 | 765                      | 40                          |
| hepatis              | 1                                | (21.6)                        | 975                 | 0.68                 | 1271                     | 58                          |
| 22 ♀ 16              | 2                                | (22.2)                        | 1000                | 0.69                 | 1029                     | 56                          |
| Febris indeterminata | 3                                | (22.3)                        | 1280                | 0.89                 | 893                      | 40                          |

The blood urea is calculated as average of 4 values; when placed within Diuresis: + after the figure indicates that a little urine has been lost. Ammonia in the urine is calculated as mg % urea.

Clst average: Standard clearance calculated by means of the average Clst 8+8: Standard clearance calculated by means of the average of 2 Clmax: 24 hour clearance is calculated as maximum clearance irrespective of diuresis. Clmax average: Calculated by means of the average of 4 determinations Clmax 8+8: Calculated by means of the average of 2 determinations

one-hour clearance was determined for most of them. The results will be seen in Table 6.

As will be seen from the table, the blood urea for all these individuals was relatively low, from 10.8 to 39.6 mg % (the average for the first twenty-four hours); as a general rule the blood urea is stated to be between 10 and 50 mg %. The low blood urea in this material may possibly be due to the fact that most of the patients prior to the experiments received hospital diet containing 83 g protein daily for the males and slightly less for the females, i. e. their diet was not particularly rich in proteins.

The daily urea output in the urine is rather low, varying from 5.8 to 21.2 g urea. We are told that the total urea output per day

| NH <sub>3</sub> in % of urea. | Urea conc. index. | g protein pr 24 hours | g protein per kg | ClSt average | ClSt 8 + 8 | Clmax average | Clmax 8 + 8 | 1-hour clearance | Urea conc. index for 1-hour clearance |
|-------------------------------|-------------------|-----------------------|------------------|--------------|------------|---------------|-------------|------------------|---------------------------------------|
| 8                             | 30                | 50.6                  | 0.72             |              | 31         |               | 32          |                  |                                       |
| 9                             | 35                | 52.0                  | 0.74             |              | 36         |               | 37          |                  |                                       |
| 7                             | 20                | 49.4                  | 0.70             |              | 23         |               | 26          |                  |                                       |
| 3                             | 118               | 50.6                  | 0.95             | 72           | 74         | 44            | 45          | 50               | 9                                     |
| 9                             | 40                | 49.8                  | 0.94             | 41           | 44         | 41            | 44          |                  |                                       |
| 16                            | 33                | 47.2                  | 1.06             | 31           | 31         | 29            | 29          | 59               | 10                                    |
|                               | 71                | 45.0                  | 1.01             | 48           | 47         | 33            | 32          |                  |                                       |
| 3                             | 52                | 38.3                  | 0.87             |              | 33         |               | 31          |                  |                                       |
| 6                             | 37                | 50.6                  | 0.90             | 37           | 37         | 37            | 37          | 71               | 40                                    |
| 8                             | 55                | 51.5                  | 0.92             | 43           | 42         | 34            | 33          | 69               | 10                                    |
| 10                            | 39                | 53.2                  | 0.95             | 38           | 37         | 38            | 36          |                  |                                       |
| 7                             | 44                | 47.4                  |                  |              | 37         |               | 31          | 55               | 15                                    |
| 10                            | 43                | 46.7                  |                  |              | 34         |               | 27          |                  |                                       |
|                               | 35                | 45.5                  |                  |              | 28         |               | 22          |                  |                                       |
| 6                             | 44                | 50.6                  | 0.52             | 37           | 35         | 32            | 30          |                  |                                       |
| 5                             | 35                | 49.8                  | 0.53             | 36           | 36         | 36            | 36          |                  |                                       |
| 5                             | 59                | 50.6                  | 0.94             |              | 48         |               | 40          | 51               | 6                                     |
| 5                             | 46                | 48.5                  | 0.91             |              | 39         |               | 32          |                  |                                       |
| 4                             | 40                | 49.4                  | 0.92             |              | 38         |               | 36          |                  |                                       |

brackets the figures indicating blood urea represent the average of 2 values.

of 4 determinations of blood urea.  
determinations of blood urea.  
pective of the volume of the diuresis.  
of blood urea.  
of blood urea.

is about 30 g when the diet contains 118 g proteins (Handbuch der normalen und pathologischen Physiologie). Presumably the low urea output is connected with the relatively low protein metabolism and the low blood urea.

If 118 g ingested protein gives an output of 30 g urea, 50 g protein will give 13 g, and this agrees with the urea output of the patients in this experiment.

The amount of ammonia in the urine varies a good deal; the content of ammonia in the urine being dependent first and foremost on the urine reaction (which was not recorded), it is difficult to suggest any case of these variations. In certain cases the ammonia formed a relatively high percentage of the urea (maximum 16 per cent.); this



may be due to the fact that the nitrogen output on a protein-poor diet is conditioned mainly by a fall in the urea output and the ammonia content in the urine falls proportionately less.<sup>1</sup>

Of the values given the maximum twenty-four clearance is of the greatest interest as an expression of the twenty-four hour function of the kidneys. The greatest variation in the maximum clearance of an individual is from 21 to 31, i. e. a fluctuation of  $\pm 19$  per cent. (Patient No. 2 is disregarded; the clearance varied from 14 to 27, possibly a diuretic error?). On an average the variation is  $\pm 8$  per cent. For comparison I may add that the maximum clearance of Eggert Møller, McIntosh and Van Slyke's individuals displays fluctuations from their average clearance of up to  $+31$  and  $-20$  per cent.

The absolute variation in the twenty-four hour maximum clearance of the normal individuals is from 21 to 68 if we omit the lowest clearance of 14 (diuretic error?).

For all patients the maximum twenty-four clearance is lower than the one-hour maximum clearance. The reason for this is that in the case of the one-hour clearance after water ingestion the diuresis is high and the concentration index for urea low, whereas the twenty-four diuresis per time-unit is lower and the concentration index for urea high; thus in the latter case much more urea will pass back through the tubuli.

| Patient | One-hour clearance | Twenty-four hour clearance maximum | Urea concentration index |
|---------|--------------------|------------------------------------|--------------------------|
| 7       | 68                 | 66                                 | 81                       |
|         | 64                 | 58                                 | 73                       |
|         |                    | 58                                 | 90                       |
|         |                    | 53                                 | 83                       |
| 15      | 61                 | 36                                 | 96                       |
|         |                    | 37                                 | 108                      |
|         |                    | 44                                 | 78                       |
| 9       | 54                 | 47                                 | 38                       |
|         |                    | 48                                 | 60                       |
| 20      | 55                 | 31                                 | 44                       |
|         |                    | 27                                 | 43                       |
|         |                    | 22                                 | 35                       |

<sup>1</sup> It must be due to an analytical error that the ammonia content for the first five patients is 0, as normally there are always small quantities; only in the case of alkalosis induced by ingestion of alkali or in the case of hyperventilation is there an absence of ammonia in the urine.

It appears that patients with the same one-hour clearance may have different twenty-four hour clearances, even in those cases where the concentration index for the two patients is fairly equal. This will be seen on comparing Patients Nos. 7 and 15 and Nos. 9 and 20.

Patient No. 15 is up, which may be the reason why his twenty-four hour clearance is lower than No. 7's. This does not apply to Nos. 9 and 20, however, as both are confined to bed.

Furthermore, patients who by their one-hour clearance reveal a difference in their renal function may have almost the same twenty-four hour clearance and the same concentration index for urea; this is so for instance with patients Nos. 6 and 7:

| Patient | One-hour clearance | Twenty-four hour clearance | Urea concentration index |
|---------|--------------------|----------------------------|--------------------------|
| 6       | 94                 | 62                         | 92                       |
|         | 79                 | 65                         | 79                       |
|         |                    | 53                         | 105                      |
| 7       | 68                 | 66                         | 81                       |
|         | 64                 | 58                         | 73                       |
|         |                    | 58                         | 90                       |
|         |                    | 53                         | 83                       |

This shows either that filtration, which is expressed by the one-hour clearance, may vary in the course of the twenty-four hours, whereby a single one-hour test is no expression of the total function in the whole day, or that tubular reabsorption was different for the two patients.

Nevertheless it does happen that the twenty-four hour clearance and the one-hour clearance of two different patients will also give fairly equal results both in cases where  $C_u$  is the same for the two patients (20 and 22) and where  $C_u$  is different (15 and 18). — On the whole there is a certain proportionality between the maximum twentyfour hour clearance and the one-hour clearance (graph 5).

A twenty-four hour functional test of this kind gives rise to many problems regarding the functioning of the kidney, and there is reason for presuming that more extensive investigations will be capable of producing a good deal of information that cannot be obtained by means of a one-hour test alone.

## Summary.

The purpose of this investigation was to devise a renal-function test to express the total function of the kidneys in the course of twenty-four hours.

Blood-urea analyses were made for four healthy individuals on ordinary diet, and it was found that the urea varies greatly in the course of the twenty-four hours. By altering the diet so it contains less protein it was found in eight individuals by means of nine blood-urea analyses in the twenty-four hours that there were much smaller fluctuations.

A diet was then composed containing 50 g protein, and with this it was found possible to keep the blood urea of 37 individuals relatively constant during the twenty-four hours. On measuring the blood urea two mornings running on this diet one can obtain an expression of the average blood-urea value for the whole day. In 91 per cent. of the tests made the average blood urea for the two mornings showed a deviation of  $\pm 6$  per cent. from the actual average.

An examination was made of the twenty-four hour urea clearance of 22 individuals and the results compared with the ordinary one-hour clearance. When repeated tests of the twenty-four hour clearance are made for the same individual one finds variations of dimensions similar to those in the one-hour clearances. The absolute value of the maximum twenty-four hour clearance in different individuals varies between 21 and 68. On the whole I find a certain proportionality between the twenty-four hour clearance and the one-hour clearance. On the other hand, individuals having the same one-hour clearance may have different twentyfour hour clearances, and vice versa.

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My grateful thanks are due to Miss Andrea Eriksen, steward of the Kommunehospital for assistance in arranging the diet.

(From the Children's Department, Borås Hospital, Sweden: Physician-in-charge: Dr B. Söderling, and Västeråsen Sanatorium: Physician-in-charge: Dr E. Törnell).

## Intrathoracic Malformations in Young Children.

By

B. SÖDERLING and R. THUNE.

(Submitted for publication October 22, 1942).

### I. A case of cystic lungs in a 14-months-old girl.

During recent years an increasing number of congenital cystic lung changes have been described. Therefore, from having had on the whole only a pathological-anatomical interest earlier, they have become of increased diagnostic interest, and in a number of cases also of therapeutic interest.

The changes may vary in size and extension from being so pronounced that they are incompatible with continued life, to small ones which give rise to no symptoms at all throughout life.

Various explanations have been given of the origin of the cystic lung, and a number of names used all in accordance with conceptions as to the nature of the complaint, e. g. bronchial or lung adenoma, fetal bronchiectases, congenital lymphangiectases, etc. It is probably not a question of a genetic unit (Kahlsdorf). Therefore in general a more neutral collective designation has begun to be used: *congenital cystic lung on a malformation basis*.

The cysts vary in number and size, all according to at which period of fetal life the disturbance in development began. If it took place early, occasional larger cysts originate from the bronchial rudiment; if it takes place later from the finer bronchial branches, the cysts are smaller.

If the development is generalised, a type appears which is usually called «sponge lungs» on account of its appearance, its section surface resembling in appearance a large-pored toilet sponge.

A case with pronounced bilateral sponge lungs, which did not show any symptoms until the age of 14 months, may be worth describing somewhat more in detail.

It is the case of a girl child born 1/8 1939, who was admitted to the Children's Department at Borås Hospital on 28/9 1940.

Patient the only child. Mother healthy, with W. R. neg. Child's weight at birth 4,080 g. Received breast milk only for one month; mixed feeding later. First tooth appeared at age of 4 months.

At the age of 8 months she began to have small scurfy papules on the scalp and on the back. Began to be fidgetful, did not eat so well and cried on urination. Examined by the medical officer, who diagnosed pyuria and a certain amount of neglect.

When she was admitted on 28/9 1940 to the Children's Department, the examination showed a pale child with flabby flesh. In the folds of the skin there were very badly tended skin changes, with large patches of caked powder and secretion. Vulva dirty and stuck together. Over the abdomen and on the scalp numerous scattered papules crusted with powder, partly with the tops rubbed off.

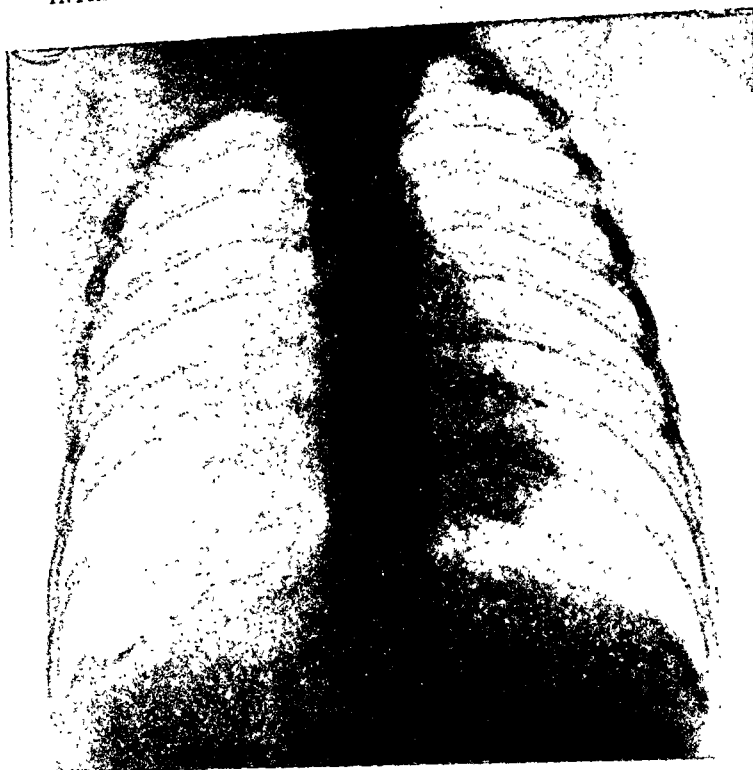
She also exhibited signs of rachitis with well-developed rachitic rosaries and irregular teeth.

Weight 8,850 g. Afebrile. The urine exhibited nothing palpably pathological. A blood examination indicated slight anemia and leukocytosis (15,900).

The day after admission an obvious dyspnoea was observed with *ala nasi* breathing and inspiratory concavities at *angulus costae*. The lungs exhibited a tympanitic tone and reduced breathing sounds.

On 6/10, i. e. 9 days after admission, the child was extremely dyspneic and troubled in her breathing. She lay with severe *ala nasi* breathing and pronounced concavities at *angulus costae* and strong abdominal respiration. General condition affected. Temp. 38°. Pulse 140. Physical examination of the lungs: extremely high tone and weak respiratory sound. Everywhere, principally over the posterior sides, small hard râles. At M. on the left side intensified broncho-vesicular respiratory sounds. The symptom picture gave the impression of a bilateral pneumothorax. A roentgen examination was made, the following report being given: «The diaphragm arch is greatly displaced downwards and obliterated and only makes small movements. Within the lung areas a pronounced bullous emphysema.» (See picture 1.).

Her condition deteriorated, and after 24 hours death supervened after increasing difficulties in breathing.



Picture 1.

*Pathological-anatomical examination of the lungs* (Professor Reuterwall).

Macroscopic pronouncement: (See Picture 2). The lungs are voluminous. On the surface dense emphysema-like vesicles, varying in size from that of a hemp seed to that of a walnut, at places conglomerate. The most pronounced changes corresponding to the upper lobes of the lungs and over the middle lobe of the right lung. The latter is bullously changed in its entirety. In section through the different lobes on the whole a homogeneous picture. The lung tissues are like a large-pored toilet sponge. Larger and smaller cystic lumina, smooth-walled, partly confluent, in places only separated by thin membranes, in places again by an obviously air-bearing parenchymal layer of varying thickness. In this, within smaller areas, macular changes, as in the upper lobe of the right lung, (see below). No fluid in the cyst-like lumina. In the lower part of the upper lobe of the right lung the parenchyma is largely solid, spotted greyish-white, firm, not air-bearing. In section the bronchi are thick-walled with fairly narrow lumina. Trachea and main bronchi without noteworthy changes. No stenoses

No deformities in the heart

Microscopic examination:

1. From the lower lobe of the left lung: larger and smaller cyst-like lumina. Only one here and there is covered with low cylindrical, light epithelium, partly replaced with a layer of multinuclear giant cells. For the most part there is no specific epithelial covering. Around the cyst lumina



Picture 2.

a tissue of fairly polymorphous appearance abundant in capillaries and cells: fibroblast-like cells, large rounded monocytic cell elements, cells of lymphocytic type. In places here and there a plasma cell and an occasional polymorphous nuclear leukocyte. Between these greatly changed areas there are well-developed, partly emphysematous lung parenchymas. In these foci of pneumonic changes: serous exudation, desquamative cells, in some places occasional polymorphous nuclear leukocytes in the alveola. In the lumen of a number of bronchi abundant leukocytic exudate.

II. From the lower part of the upper lobe of the right lung: the macular greyish-white portions exhibit the same pictures as the tissue round the cyst-like lumina. (see above). No necroses. No tubercle-like structures. No noteworthy vessel changes.

Reuterwall writes as a summary of the examination: »There are here pictures similar to those seen with congenital cystic lung on the basis of malformation. The somewhat polymorphous pictures in places resembling pneumonia alba in certain respects give reason, however, to raise the question whether a luetic lung affection may be present.»

As the question whether a luetic change is present may be excluded, since the mother exhibits a negative Wassermann reaction, it appears that this is a typical case of congenital cystic lung malformation of polycystic type.

### Commentary.

As is mentioned in the introduction, the etiology of the congenital cystic changes is not known with certainty. In any case, however, they appear to be the result of a degenerative process (Wacharressa), which may also affect other organs, such as the kidneys. Bergh, Nilsson and Zachrisson have described some interesting cases where diffuse cystic lung changes appeared simultaneously with a tuberous cerebral sclerosis.

Lung cysts may be solitary or multiple, and may be filled with fluid or air. At birth the cysts contain a serous, transparent, yellow fluid. If there is no connection with a bronchial tube, the fluid remains there; if there is a connection it becomes air-bearing. (Adams-Swanson). The airbearing cysts may be enlarged later by the ventilation mechanism (Schenk).

The pathol. anat. picture may vary considerably in congenital cysts. Hennel divides the changes into two main groups according to their structure:

1. Cysts the origin of which can be traced from the bronchial ramifications with concentrically arranged muscle fibres and cartilage, and covered with cilia-bearing high epithelium.

2. Cysts which wholly resemble emphysema vesicles.

Between these two main types there are all the transition forms, solitary or multiple cysts surrounded by a polymorphous mesenchymal tissue.

In a number of cases where the changes are less pronounced, and secondary inflammatory processes have set in, it may be difficult to distinguish them from acquired bronchiectases.

The symptom picture varies with the size and diffusion of the cysts. Small and sparse cysts do not necessarily show any morbid signs unless an infection sets in.

Even with more extensive changes, symptoms may not appear at first. Not until the functioning parenchyma has been reduced by



the enlargement of the air-bearing cysts owing to a ventilation mechanism, or by its becoming the seat of inflammatory processes, does the affection become manifest. An enlargement of the cysts may also be conceived as due to a growth *e vacuo* following on the disproportion between a normally growing thorax and a deficient lung due to malformation (Herms and Mumne).

The most usual symptom is attacks of dyspnoea, which may become extreme with auxiliary respiratory movements. At the same time an appreciable cyanosis is often observed. Among the ordinary symptoms is also coughing. Occasionally hemoptysis appears, which is often wrongly interpreted as being due to lung tuberculosis. The dyspnoea and cough may also mislead the doctor to diagnose asthma. The clinical picture often permits of the presumption of a spontaneous pneumothorax.

With the help of the anamnesis and clinical findings, the diagnosis may be presumed. Therefore the congenital cystic lung should be borne in mind in the case of attacks of dyspnoea and cyanosis in children, when more serious affections of the air-passages have not been met with previously, and where the condition does not tally with observable affections of the air-passages.

Roentgen may give a probable diagnosis by establishing the cystic formations in the lung. But the proof of a cystic change alone is not sufficient to establish the diagnosis of cystic lung in the restricted sense. It may often be difficult to distinguish between ordinary bronchiectases and congenital cystic changes. This difficulty can be overcome to some extent by the observation of the size, shape and localisation. Multiple cysts of congenital nature may give the picture a sponge-like, often coarse-meshed structure of ring shadows with sharp outlines. The surroundings show no signs of inflammatory processes, nor are there any signs of shrivelling. In the case of the sac-shaped bronchiectases, the cavities are often smaller, not so sharply delimited, and more or less clearly grouped in association with an affected bronchial branch. Most frequently inflammatory changes round the bronchiectatic cavities are also seen (Schenk). The prognosis is dependent on the number and size of the cysts and on possible complications. On the whole, if the changes are so extensive that they give rise to symptoms already in the early years of childhood, the prognosis is always poor.

With regard to treatment, it will most frequently be symptomatic. In a number of cases with localised, defined changes, puncture, drainage, and sometimes lobectomy have given good results.

*Summary:* A 14-months'-old girl is admitted for an insignificant commonplace complaint. From the very beginning a certain dyspnoea is observed, which does not correspond to that of fever, heart or lung complaints, etc. (at ordinary clinical routine examination). In association with an infection of the upper air-passages, the patient's respiration becomes extraordinarily affected and gives the impression — even on physical examination of the lungs — of a bilateral spontaneous pneumothorax. Rtg. examination gives the result — cystic lungs (?). The child dies after 24 hours. The path.-anat. examination verifies the rtg. diagnosis.

In connection with the case, clinical, roentgenological and path.-anatomical commentary.

## II. A case of a large pleural tumour (local malformation?, dermoid?) in a 1½-years-old boy.

Thoracoscopy — extirpation — recovery.

Case H. K. Borås Hospital, Children's Department 462/41. Born 29/12 1939. Nursed 1/8—10/9 1941. Father of unsound mind, for the rest nothing of hereditary interest. Normal confinement. Weight at birth 3,620 g. Breast-fed for 9 months. Control at Infant Welfare Centre. During the spring of 1941 measles and subsequently repeated periods of catarrh in the air-passages, which prevented visits to the Welfare Centre. During a stay in the country, a specially severe such infection period. A doctor who was called in the diagnosed *water in the pleural sac* and advised the family to go to the dispensary in their home district. They went home and the child was admitted to the Children's Department, Borås Hospital on 1/8 1941. Amnestically the vague details arouse a certain interest. It was not possible definitely to observe any breathlessness, nor any more exact point of time for an onset, which would indicate an inflammation of the pleural sac. There had been some days of moderate fever and a slight cough occasion ally during the spring. No protracted periods of fever with dis-improved general condition. Even the last period had been fairly brief.

*On admission:* entirely free of fever, weight 11.3, slender build, pale, reduced turgor, unaffected. Insignificant, loose cough. *Thorax:* bulging left side with prominent interstices between the ribs. No, or very small, thoracic respiration movements on the left side. The heart strongly displaced to the right. Massive dulness on the whole of the left side with ab-

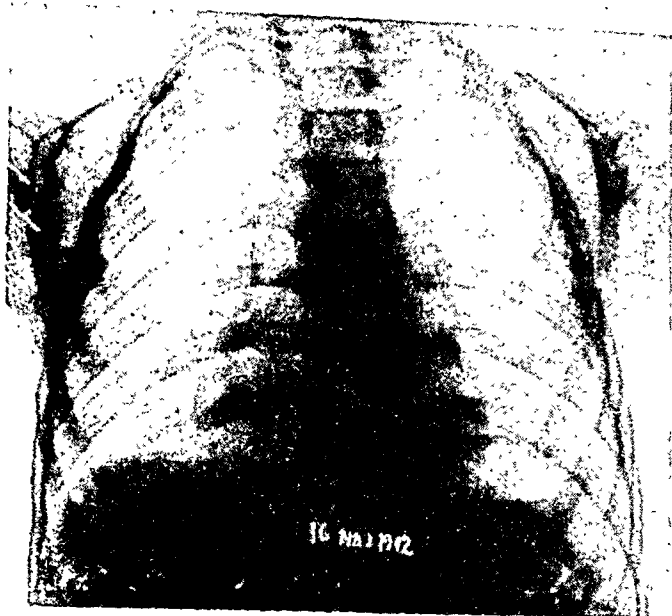


Picture 3.

sent to greatly decreased respiration sounds. From the internal organs for the rest nothing worthy of note. *Mantoux* 1/100: neg. *Blood*: Hb 87 %<sub>100</sub>, red blood corpuscles 5.3 mill., white 15,300. Diff: N: staff nuclear. 14 %, segm. nuclear 54 %, Lymph. 28.5 %, Monoc. 3.5 %. *S. R.*: 6 mm/lhr. *Rtg.* reveals large exudate shadow. *Test puncture* of the pleura: strange greyish-brown fluid of the consistency of thin cream. Strong fibrin content. Microscopically without notable findings. No bacterial growth on cultivation.

*Course*: Consistently good general condition, free of fever and bright. Thoracocenteses of 4—500 cm<sup>3</sup> of but little value, as the fluid cavity fills again, and as the patient is a little troubled *before* as *after* the tappings. Respiration frequency constant between 22—26 per minute. On 29/8 drainage performed, according to Bülow, with a catheter (no. 15) inserted in the pleural cavity and retained there during 24 hours. After the catheter was removed the exudate rapidly formed again. As the whole picture diverged from the ordinary exudate type, *thoracoscopy* was performed (6/9) with the assistance of a colleague. The following report was then given: »Puncture in the axillary line somewhat below the axilla. Paracentesis and lavage of exudate. At thoracoscopy an irregular tumour was observed, which in certain places had growths like bunches of grapes, in other places was coated with a fibrin-like membrane. The tumour extended chiefly posteriorly-upwards, but also medially. Adhesions were to be seen at a number of places in the outer edges. The thoracal wall was reddened and undifferentiated. Diagnosis: tumour (teratoma?)». (Dr E. Törnell, Väs-





Picture 5.

Further, there were mucus-secreting, branched tubular glands covered with cylinder epithelium, which opened into the laminated epithelium-covered cysts. These glands were surrounded by a loose myxomatous connective tissue resembling that seen in a fibroadenoma mammae. It is open to question how a tumour of this sort is to be apprehended. On the one hand it is possible that it is a question of a teratoma, on the other, the possibility cannot be excluded that it is a matter of a simpler local malformation. For my part I am inclined to associate myself with the latter interpretation. In that case it is here a matter of a heteropathic skin and mammary tissue. The histological sections speak strongly in favour of this, as skin and mammary-like tissue is the only thing observed. Pulmonal epithelium, intestinal epithelium, nerve system, musculature etc. were entirely absent.»

At later controls it was established that the growth and general condition were very satisfactory. The last examination was made on 16/5 42. It then proved (picture 5) that *the lung on the operated side had now developed*, and that a normal roentgen lung volume appeared to be present there. At the immediately preceding lung control this had not yet been the case (see picture 4). At the physical examination strong respiration sounds were established over the side which had previously been practically silent.

In many respects the case is probably unique, but it does not therefore lack practical interest, for when one is faced with the isolated case — however rare it may be — it is obvious that something must be done, in the first place to clear up the diagnosis, and

in the second therapeutically to master in the end a condition which cannot be dealt with conservatively. The above satisfactory diagnostic and operative results must, then, appear to be encouraging. The literature on cases of this category deals mainly with dermoids, which does not make any material difference in practice, (Nor can the possibility of a dermoid be excluded in our case).

In 1935 Hammarskjöld published a lengthy monograph, in which he had collocated from the literature 163 cases of intrathoracic dermoids which had been published up to that time, and he himself reported 9 Swedish cases. It appears from the casuistics that only 18 of the 172 cases were children under 15 years. In view of the etiology, this is remarkable. It might have been expected that the material would have consisted to a much greater extent of young patients, as the disease must be apprehended as congenital. It is obvious that, in the majority of cases, some other factor is required for this malformation to make itself clinically noticeable. The first thing that suggests itself is to suspect a probable onset of an infection from the air-passages. This can never be anything but guesswork which cannot be verified, but it is supported by the numerous prolonged cases of bronchitis which are encountered.

According to Hammarskjöld, 6 cases of such tumours were met with in 1935 in *infants* and *small children*. The patients were children of the age of 4 months (Poynton & Monerieff, 1929), 6 months (Willcox & Wollstein, 1931), 2 years (Carpenter, 1906), 3 years (Hedblom, 1933), 4 years (v. Török, 1900, Smith & Stone, 1924). Half the cases were treated surgically, but only the child operated on in two stages by Hedblom survived (and recovered completely), both the others and all those treated conservatively, died within relatively short periods from respiration — circulation troubles.

In the majority of the 172 cases, the most pronounced symptoms were cyanosis, dyspnoea and coughing. Among the children these appeared with particular regularity. In our case there was only an inconsiderable loose bronchitis. Further, it is worthy of note that the occurrence of large pleural exudates was not infrequently the immediate cause of the hospital treatment, the diagnosis, quite naturally, being sometimes wrongly made as pleuritis exsud. tbc. treatment at sanatoria etc. being ordered. Among these were, for instance, Hammarskjöld's own case IX and Becker's case

(1927). These were also the only ones in which thoracoscopy was resorted to later in order to establish the diagnosis definitively.

*Summary.* We were confronted with a case of total exudate in the left pleura in a 1 ½-years-old child, and there were many reasons to suspect a benignant tumour or a malformation growth as the cause of the exudate. The anamnesis was extremely diffuse, the boy's freedom from fever, unaffected general condition, low S. R., tuberculin negativity, the appearance and sterility of the exudate, and finally, the respiratory conditions, made this assumption extremely probable. With regard to the last-mentioned, the observation that the respiration frequency was maintained around a fairly ordinary value, i. e. about 22—26 respirations per minute, *independent of the distention of the pleural cavity with fluid* is worthy of attention. It seemed as though the patient had had an opportunity over a long period to adapt himself to the increased respiratory strain, and as though the exudate did not noticeably increase an already voluminous process. The successful thoracoscopy which confirmed the diagnosis and explained the roentgen picture, as well as the result of the one operation, which was excellent, in spite of the great diffusion of the tumour and the difficult adhesion conditions, indicates encouraging possibilities in the case of even very small patients. The capacity of the lung gradually to develop — as it appears — its ordinary volume demonstrates the satisfactory power of restitution. In this case for an unknown period — it may be estimated as at least 1 year — the lung had been collapsed by compression and absolutely without function.

#### Litterature.

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From the Municipal Hospital in Bergen, (Norway) Medical Department  
Physician-in Chief: Gunnar Bøe M. D.

## Acute hemolytic Anemia.

2 cases of Lederer type.

By

PER HANSSEN.

(Submitted for publication November 8, 1942.)

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In 1927 P. F. Holst recorded a case of hemolytic anemia under the title »Sur les anémies hémolytiques non registrables». This special designation was meant to draw attention to the cases of hemolytic anemia, acute as well as chronic, which on the one side could be distinguished from the typical cases of pernicious anemia and hemolytic icterus, but which were, on the other hand, not yet sufficiently well known to have obtained a uniform designation.

In the past years a great number of cases of acute hemolytic anemia have been published, and it appears, particularly after the papers of Lederer in 1925 and 1930, as if a definite type is distinguishable, viz. the Lederer anemia, even if all investigators do not yet agree that this is an entity of disease. I shall report two cases as a contribution to the clinic of the acute hemolytic anemias, especially as several examinations of sternal bone marrow have been carried out in the one case, and in both cases transient reduction was found of the osmotic resistance of the red blood cells.

In recent years several reviews have been published of cases belonging to this special type of anemia, thus in 1937 by Giordani and Blum, in 1938 by Greenwald, and in 1940 by Dameshek and Schwarz. The two latter authors state that since 1907 approximately one hundred cases have been reported by eighty observers.



In the northern countries one case each has been published by: P. F. Holst (1927), Tage Christiansen (1929), Lars-Gøsta Sterner (1941), Knud Høyer (1941), and K. Kjellberg (1941).

Dameshek and Schwarz enumerate the following important diagnostic points:

1) History of acute or fairly acute onset usually with gastrointestinal symptoms, rapidly progressive pallor and weakness.

2) Signs of marked anemia with definite icterus and splenomegaly.

3) Evidences in the blood of severe anemia often described as macrocytic in variety.

4) Signs of increased blood formation, leucocytosis, young granulocytes, polychromatophilia, reticulocytosis, nucleated red cells.

5) Evidence in the body fluids of increased blood destruction, such as bilirubinemia, increased bilirubin output in the stools and urine.

6) Evidence against pernicious anemia such as absence of central nervous system phenomena and glossitis and presence of free hydrochloric acid in the gastric juice.

7) Lack of demonstrable or obvious cause for the hemolytic process such as bacteria, chemicals, neoplasms and pregnancy.

8) Complete absence of similar disease in the family.

In addition to these eight points should be mentioned that blood transfusion in most cases «cures» the disease in the course of a brief time, even if the same «cure» may occur spontaneously. For a detailed report of the separate symptoms reference is made to one of the above mentioned reviews.

In recent years the knowledge of the clinic and hematology of the pernicious anemia has been so considerably increased that it is rarely possible to confuse this lesion with the Lederer anemia. If, on the contrary, the first attack of hemolytic icterus gives clinical symptoms during an acute exacerbation of the disease, the differential diagnosis may be almost impossible if no opportunity offers of observation for some time.

**Case no 1.** — 507/31 — Male, born 1911.

In hospital October 15—December 14. 1931.

He is aware of no similar cases of disease in the family. He has always been pale and thin. Two years prior to admission he had been under ob-

servation in a tuberculosis sanatorium, without any sign of active pulmonary tuberculosis having been discovered, however. 2—3 weeks before admission he caught an intense cold with coughing, went to work, however, until four days prior to admission. Three days before admission he developed a violent headache with rise in temperature. Confined to bed for the past two days. At the same time he noticed that the urine was hemorrhagic, and that he was yellow in the face. He was admitted into the Surgical Department under the diagnosis fever — hematuria, and after four days he was transferred to the Medical Department under the diagnosis sepsis — hemoglobinuria.

When admitted into the Surgical Department he looked extremely ill, yellowish pale, and was complaining of violent headache. Temperature 39.4° C., pulse 112 regular. Slightly icteric skin and mucous membranes. Lungs and heart: normal physical conditions. The spleen is palpable just below the costal margin. The liver could not be palpated. No glandular swelling. Urine: albumin, pus, sugar, all negative, but guajak test positive. Microscopically were found some white blood cells, no red blood cells.

In order to facilitate the survey the description of the further clinical course and the supplementary laboratory examinations have been recorded under separate headings.

#### *Hematological examinations.*

(The hematological terminology is the identical one to that used by Naegeli and Schulten.)

On diagram no. 1 have been entered hemoglobin values, counts of red and white blood corpuscles as well as reticulocytes during the first part of the hospitalization. On the same diagram have been included also the values of serum colour and the determinations of urobilin in the urine. The diagram demonstrates the rapid fall in the values for white blood cells and reticulocytes simultaneously with the temperature becoming normal. During the same period the values of hemoglobin and the red cells increase rapidly. The rise also continues after the period comprised by the diagram. The examination on November 23rd showed a hemoglobin percentage of 72, red cells 4.67 millions, white cells 6,300, on december 5th hemoglobin 78 per cent, red cells 6.12 millions, white cells 5,300.

Smear of peripheral blood, October 17: Approximately one-fifth of the 60,000 «whites» blood corpuscles are nucleated red cells, essentially normoblasts, though also considerable numbers of macroblasts. Severe anisocytosis, the smallest diameter on micrometry being 4.6 micron, average diameter 6.7 micron, and largest diameter 10.2 micron. The differential count showed 6 per cent myelocytes, and further also several immature neutrophils. Smear, October 22: Still some normoblasts, though a much lower percentage than on October 17th. Still anisocytosis. Particularly the microcytosis, however, less pronounced. 8 per cent myelocytes.

Smear, October 29: The red blood cells are normal apart from slight aniso-poikilocytosis. No nucleated red blood cells. The differential count shows normal distribution apart from 39 per cent of «stab» neutrophils.

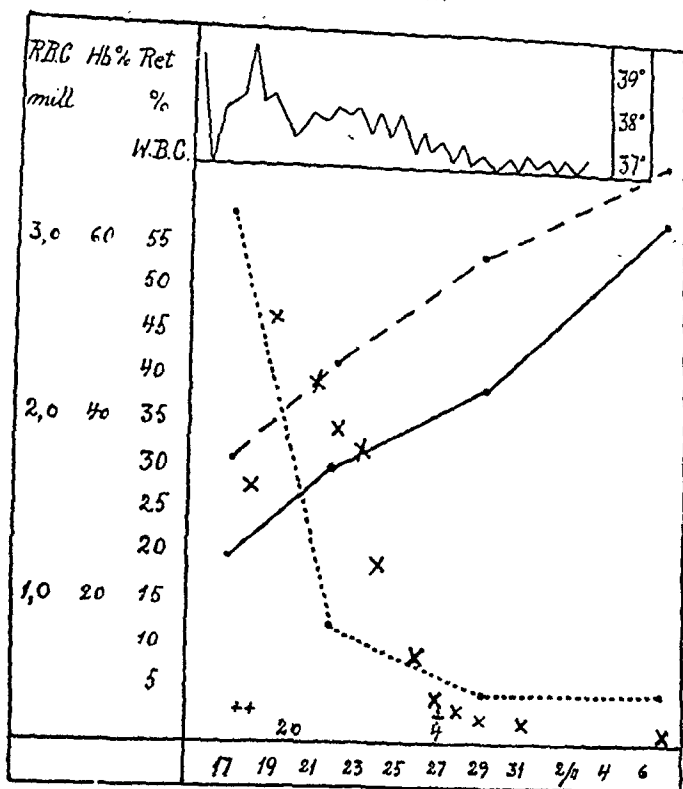


Diagram 1.

The unbroken line indicates the hemoglobin values. The broken line the number of red blood cells. The dotted line the white blood cells. The crosses give the values of the reticulocytes.

Smear, November 23. and December 5. showed entirely normal conditions. October 29. Thrombocytes 213,000/mm<sup>3</sup> blood.

November 2. Micrometry: Smallest diameter 6.5 micron

Average » 7.3 »

Largest » 9.3 »

Osmotic resistance October 22. Incipient hemolysis 0.58 per cent NaCl.

Complete » 0.42 » » »

October 19. Serum shows severe hemolysis, oxyhemoglobin demonstrated spectroscopically.

October 19. No growth in blood cultures. Serological syphilis reactions negative.

November 16. Sedimentation rate of red blood cells 13 mm/1 hour.

*Urine examinations.*

During the first days in hospital the urine was strongly hemorrhagic with large brown sediment. Guajak test positive. Microscopically some scattered red blood corpuscles. Spectroscopically oxyhemoglobin was found in the urine. After October 21st no blood in the urine.

The X-ray examination of the lungs on November 18th showed some

|                            |   | 27/8 | 30/8 | 3/10 |
|----------------------------|---|------|------|------|
| Proerythroblasts .....     | % | 7.5  | 3    | 0    |
| Macroblasts .....          | % | 15   | 78.5 | 5.5  |
| Normoblasts .....          | % | 30.5 | 179  | 16.5 |
| Myeloblasts .....          | % | 0    | 0.5  | 3.5  |
| Promyelocytes .....        | % | 5.5  | 9.5  | 7    |
| Myelocytes .....           | % | 8    | 11.5 | 13.5 |
| Metamyelocytes .....       | % | 12   | 9    | 10   |
| Neutrophils { stable ..... | % | 34   | 38.5 | 34.5 |
| { segment .....            | % | 21.5 | 26   | 17.5 |
| Eosinophils .....          | % | 1.5  | 1    | 4    |
| Basophils .....            | % | 0    | 0    | 0    |
| Monocytes .....            | % | 1.5  | 1    | 0    |
| Lymphocytes .....          | % | 16   | 3    | 10   |
| Plasma cells .....         | % | 2    | 0.5  | 2    |
| Reticulum cells .....      | % | 5.5  | 10   | 4    |

Differentiation of 3 smears of the sternal marrow, patient no. 2.

old spots in the supra- and infraclavicular regions of the left lung. Otherwise normal conditions.

#### *Clinical course.*

During the first days in hospital he was greatly exhausted, partly with clouded sensorium. Increased temperature, see diagram no. 1. On admission the right leg presented superficial phlebitis. This receded rapidly. Between October 20th and 25th a very rapid improvement occurred, and when the temperature had become normal around October 30th he felt quite well, with no headache. On November 16th the enlargement of the spleen had vanished completely. During the subsequent stay perfect well-being. From October 22nd to December 11th the patient was given liver extract orally, and from November 27th to December 14th also ferrum reductum  $\frac{1}{2}$  g  $\times$  3.

#### *Follow-up examination 1.*

In Surgical Department from June 10th to 22nd 1938, where appendicectomy was performed. Apart from periods with slight abdominal pain he has felt well since the previous stay in the hospital. No enlargement of the spleen or the liver.

Hemoglobin 106 per cent. Red blood cells 6.10 millions, white blood cells 6,100. Smear: Normal conditions. The sedimentation rate of the red blood cells 4 mm/1 hour.

#### *Follow-up examination 2.*

Called in for examination Januari 18th 1942. He has felt quite well since 1931. No enlargement of the spleen or the liver.

Hemoglobin 98 per cent. Red blood cells 6.24 millions, white blood

cells 7,200. Smear showed normal conditions: Reticulocytes 2 per mille. The sedimentation rate of the red blood cells 2 mm/1 hour. Serum colour 4. Osmotic resistance — Incipient hemolysis 0.42 per cent NaCl.

Complete        »        0.32        »        »        »

Urine: Albumin, sugar negative. Urobilin 1/10 ++.

**Case no. 2.** — 269/41 — Female, born 1894.

In hospital August 26th—October 4th 1941.

She is not aware of similar cases of disease in the family. Previously she has been essentially in good health, apart from probable rheumatic fever in childhood. Approximately two weeks prior to admission she commenced feeling lax and having pain in the back. She had been up and about, however, eaten with good appetite and managed her housework until 3 days before admission. The last 3 days she had been confined to bed, had had some vomitings and several loose stools daily. According to information given by her husband her sensorium had been clouded the two last days. Temperature not measured.

The examination on admission showed: The patient is thin, exceedingly pale with yellowish colour of the skin, clouded sensorium. Pulse 124 regular. Temperature 38° C. Blood pressure 125/95. Tongue moist, slightly coated, not smooth. The heart: No increased dullness. Distinct presystolic fremitus and strong presystolic murmur over the apex of the heart. The spleen is not palpable, no glandular swelling. The liver is palpable four finger-breadths below the costal margin. The edge is tender. Otherwise general physical examination showed normal conditions. Urine: Specific gravity 1017. Traces of albumin and blood. Sugar nil. Urobilin 1/10 ++. Microscopically: A few red blood cells and a few granular casts.

#### *Hematological examinations.*

Diagram no. 2 demonstrates the high values of white blood cells and reticulocytes the first days of the stay, and how these values decrease to normal at the same time as the temperature falls to normal. During the same period rapid increase in hemoglobin percentage and of the red blood cells. The increase continues also after the period comprised by the diagram. The examination on September 22 thus showed hemoglobin 65 per cent, red blood cells 3.28 millions, white blood cells 5,300. October 3rd. Hemoglobin 76 per cent, red cells 3.83 millions, white cells 5300. Smear of peripheral blood on August 26th: The majority of the red blood cells are abnormally small, well saturated, some considerably, up to three times, larger, less well saturated. No distinct oval red blood cells.

Differential count revealed two normoblasts in 200 white blood cells, 2.5 per cent myelocytes and further some immature neutrophils. Smear August 29: Red blood cells approximately as on August 26. Halometry according to Pijper (normal values 7.2 micron — 7.7 micron), average diameter 6.9 micron. Differential count: 77 nucleated red blood cells in 200 white cells, normoblasts as well as macroblasts. The distribution of the white blood cells approximately the same as on August 26.

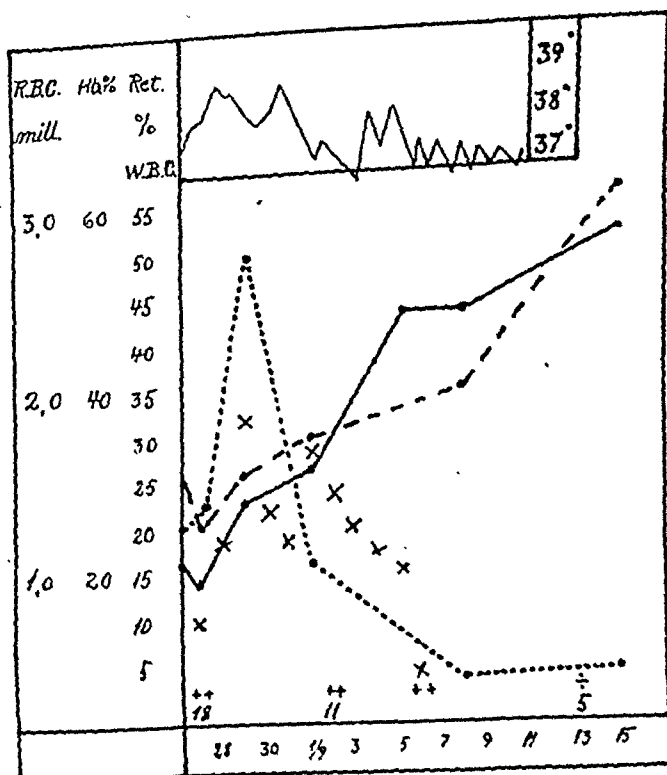


Diagram 2.

The figures at the bottom of the diagram indicate the serum colour determined by Meulengracht's method. The pathological urobilinuria is indicated in the same place by  $\div$ , +, or ++. At the top of the diagram is a temperature-chart.

Smear, September 1st: The red blood cells have changed considerably since August 26th, as there are now fewer microcytes and considerably more macrocytes. Halometry: Average diameter 9.4 micron, 20 normoblasts in 200 white cells. A few myelocytes. Otherwise, however, considerably fewer immature cells than on August 29th. Smear, September 8th: Fewer micro- and macrocytes. Still considerable anisocytosis, however. Halometry: 8.8 micron. No myelocytes and also fewer immature cells than on September 1st.

Smear, September 22nd: Distinct anisocytosis, but few micro- and macrocytes. Halometry 7.6 micron. The distribution of the white blood cells normal. No nucleated red blood cells.

During the hospitalization three examinations of sternal marrow. The result of the differential counts have been entered in the table. 200 white blood cells have been counted in each specimen, and erythroblasts and reticulum cells have been entered in proportion to 100 white blood cells in the manner recommended by Rohr in his book «Das menschliche Knochenmark».

September 13. Thrombocytes (Thomsen's method) 455,000/mm<sup>3</sup> blood. Coagulation time 9 minutes. Good retraction of the clot. Bleeding time 4 minutes.

it is particularly unfortunate that we have not had occasion to examine the remaining members of the family, as they live abroad or in other parts of Norway. Janet Vaughan, who is probably the hematologist who has been most emphatic in maintaining that cases of Lederer anemia on closer examination almost always have proved to be cases of hemolytic icterus in «crisis», demands that all members of the family should be examined, and particularly that a more accurate technic should be used for the determination of the osmotic resistance before the special diagnosis of Lederer anemia is made. In spite of the fact that these examinations have not been carried out in our two cases we are of the opinion that the diagnosis is still Lederer anemia, and that particularly the follow-up examinations, during which the clinical as well as hematological findings continually showed perfectly normal conditions, give very considerably support to this diagnosis. If the patients had had hemolytic icterus with «crisis», the different hematological signs of this disease would not be completely missing in all follow-up examinations.

The transient reduction of the osmotic resistance found in both patients at the climax of the disease, might appear to give considerable support to the diagnosis hemolytic icterus. Similar findings have been made previously, however, in definite cases of Lederer anemia (Fiessinger a. o., Josephs, Lewis, Parson and Hawksley), and too great diagnostic importance should not be attached to this transient reduction of the osmotic resistance, therefore.

In the peripheral blood of both patients signs of lively blood regeneration with many reticulocytes, immature white blood cells and nucleated red blood cells, were found at the culmination of the disease and immediately after. At the climax of the disease it was a characteristic feature also that the values of the diameter of the red blood cells showed a very great dispersion with an average diameter somewhat larger or somewhat smaller than the normal. In case no. 2 we had the opportunity by three sternal punctures to study the changes in the composition of the bone marrow. The white blood cells and the reticulum cells demonstrated no definite changes from puncture to puncture, and the recorded values did not deviate from the established normal values. The erythroblasts, on the other hand, showed considerable deviations both on August 27th and particularly on August 30th. The total figure of erythroblasts on August

27th was somewhat larger than normally, the most remarkable, however, being the surplus of proerythroblasts and macroblasts. Already on August 30th the total figure of erythroblasts had increased very considerably, though now with much fewer proerythroblasts and relatively more normoblasts. On October 3rd when the patient was well again the erythroblast figure was again normal.

On admission signs of increased hemolysis were found in both patients with increased serum colour and pathological urobilinuria. Further in case no. 1 hemoglobinemia and hemoglobinuria were present. In case no. 2 it is possible that a slight hemoglobinuria was present during the first two days in hospital.

In case no. 1 a spontaneous improvement occurred in the course of a few days after the admission into the Medical Department. This had a similar course and occurred equally rapidly as in case no. 2, who received a blood transfusion on the day following the admission. We did not see the immediate improvement after the transfusion as described by most authors, as five days elapsed before a distinct improvement occurred in case no. 2. Case no. 1 was treated with liver extract, but according to the demonstrations of Tage Christiansen and others it is hardly probable that this treatment has had any effect.

The knowledge of this special form of acute hemolytic anemia is probably of practical importance, as judging from the publications these cases increase continually. Correctly and early recognized the prognosis of this disease should be good, when the patient receive the blood transfusion necessary. Even if some patients are cured without this treatment, an unnecessary risk is involved in neglecting the blood transfusions, which are not associated with any special inconvenience to these patients.

### Summary.

As a contribution to the clinic of the acute hemolytic anemia two cases of Lederer anemia are recorded. In both cases was found a transient reduction of the osmotic resistance of the red blood cells. In the one patient three sternal marrow smears were examined, which showed a brief, but intense increase of the erythroblasts, no change in the leucoblasts or reticulum cells. The one patient was cured



quickly without special treatment. The other patient received a blood transfusion. The improvement, however, did not occur as rapidly as stated in the majority of the cases published.

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From the Department of Pediatrics of the Rigshospital, Copenhagen.  
(Chief: Professor C. E. Bloch, M. D.)

## Idiopathic Hypoprothrombinemia Refractory to Vitamin K.

By

P. PLUM.

(Submitted for publication November 6, 1942).

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The prothrombin content of the blood of normal adults lies within fairly narrow limits. With the help of his method Thordarson in a material of 104 normal adults found a variation of from 85 to 115 per cent. In previous works the author in collaboration with Hjalmar Larsen og Jacob Poulsen described two materials including 107 normal adults who were examined with Larsen and the author's modification of Quick's method. The latter of the two materials comprised 50 persons; each sample of venous blood was submitted to 10 determinations of the prothrombin time; the average of the 10 determinations varied between 17.3 seconds and 20.8 seconds. The average of the 50 10-determinations was 18.9 seconds. If the prothrombin times are converted into prothrombin percentage, the mentioned extreme values correspond to a range of from about 80 per cent to about 120 per cent. In the first-named normal material, comprising 57 persons, only 2 determinations of prothrombin time were performed on each blood sample, whence this material shows a greater variation, namely, from 15 seconds to 21 seconds.

Thordarson examined a great number of patients with medicinal diseases, and in some morbid conditions found moderate hypoprothrombinemia, namely, in uncompensated heart failure and different blood diseases, especially in myeloid leukemia; the prothrombin was only moderately reduced, in a few cases to about

50 per cent of the normal; administration of vitamin K was without effect. In the department of pediatrics of the Rigshospital prothrombin examinations were performed on 76 patients of from 1 month to 14 years of age, who did not suffer from intestinal diseases; only in cases of heart failure was, in agreement with Thordarson, found a moderate hypoprothrombinemia refractory to vitamin K.

As far as the author knows, a reduction of prothrombin has not heretofore been observed in otherwise perfectly normal, healthy individuals. Such an idiopathic hypoprothrombinemia was incidentally detected in two otherwise normal adult persons.

**Case 1**, a 20 year old married housekeeping assistant in the department of pediatrics of the Rigshospital. On the whole she had previously been healthy. A few times she had had strong and long-lasting nosebleed, but otherwise she had shown no signs of abnormal bleeding tendency. She was in the 6th month of pregnancy. The blood examination, March 6th, 1942, disclosed that the prothrombin time was 30.5 seconds (venous blood, average of 10 single determinations, see below; normal value 18 seconds). Spontaneous coagulation of recalcinated blood (ad modum Larsen and Plum) 202 seconds (normally 120—150 seconds). Thrombocytes 380,000 per mm<sup>3</sup> of plasma. Fibrinogen 0.204 per cent in plasma (Gram's method). Plasma colour below 5. Hematocrit 44. Rumpel-Leede phenomenon negative. The clot was firm. Urine without albumin, sugar, bile pigment and urobilin. Feces of normal colour. The general clinical examination revealed nothing abnormal.

| Date  | 3/6/42 | 3/9/42 | 4/21/42 | 4/22/42 | 5/13/42 | 5/15/42 | 7/11/42 | 7/18/42 | 9/4/42 |
|---|--------|--------|---------|---------|---------|---------|---------|---------|--------|
| Vitamin K (Synkavit)  |        |        | 10 mg   |         | 50 mg   |         |         |         |        |
| Prothrombin time (seconds) (venous blood, L. & P. method) . . . . | 30.5   | 30.7   | 30.0    | 27.0    |         | 27.5    | 24.0    | 28.0    | 31.5   |

*Prothrombin times in a 20 year old pregnant woman with idiopathic hypoprothrombinemia. Normal parturition July 11th, 42.*

As is seen from the table, the administration of large doses of vitamin K had but a slight effect on the prothrombin time. On parturition and 7 days later the prothrombin time was somewhat shorter, and 6 weeks after parturition it was lower than during pregnancy. It is known that a fairly considerable hyperprothrombinemia up to 200 per cent of the normal is found in normal pregnant women; with the technic here applied were found values of from 12 to 16 seconds in normal pregnant women. The prothrombin content in the child's blood was normal, being 38, 42, 39, and 27 seconds, respectively on birth and 2, 3, and 6 days later. The

prothrombin of the mother was examined on Sept. 4th both with Larsen and Plum's and with Thordarson's method, the latter revealing a prothrombin content of 34 per cent of normal, i. e. a fairly considerable decrease.

**Case 2**, an 18 year old man, living in Copenhagen under good social conditions. He had always been healthy, especially never suffered from jaundice or dyspepsia; nor had he ever noticed any abnormal bleeding tendency. Idiopathic hypoprothrombinemia was disclosed incidentally. *Blood examination* on June 6th, 1941: Prothrombin time 28 seconds. 24 hours after administration of 10 mg of synkavit 29 seconds. On August 30th, 41: 27 seconds (venous blood, L. & P.'s method, normal value 18 seconds). Converted into percentage of normal the quoted times correspond to about 50 per cent. Spontaneous coagulation of recalcinated blood (ad modum Larsen and Plum) 257 seconds (normal value 120—150 seconds). Capillary resistance (Bexelius): No petechiae. Thrombocytes 300,000 per mm<sup>3</sup> of plasma. Plasma ascorbic acid (Farmer and Abt) 0.48 mg %. Hb. 120 per cent. Feces of normal colour, without blood. Urine without albumin, sugar, urobilin and bile pigment. The general clinical examination disclosed nothing abnormal.

Thus in two young, otherwise perfectly healthy and normal individuals a distinct decrease of the prothrombin to 34 and 50 per cent, respectively, of the normal was found. These values cannot be considered as lying at the lower limit of the normal, for there is no gradual transition between them and the lowest values in a fairly great material of normals. Pronounced bleeding tendency was not found in any of the cases. In both cases the administration of vitamin K had but little effect on the prothrombin, namely, about the same effect as in normal persons, where the prothrombin time with the help of large doses of vitamin K can be reduced about  $\frac{1}{2}$  to 1 second (Plum and Poulsen). The female had higher prothrombin values during pregnancy, just as normal individuals. Thus it seems as though the prothrombin in these two individuals merely lies on a lower level than normal, otherwise being regulated in the normal manner.

The prothrombin response to administration of vitamin K is used as a help in the differential diagnosis between parenchymatous and obstructive jaundice. A number of authors have studied this problem (a. o. Tage-Hansen, Thordarson, Koller, Begtrup & From Hansen, Hult, Lord & Andrus, Wilson, Olwin & Ziffren, Owen, Warner & Peterson), and it can now be said that this liver function test is of considerable clinical value. However, as was emphasized by Begtrup and From Hansen, the occurrence is not quite rare of

cases of hypoprothrombinemia refractory to vitamin K, which is not due to a lesion of the liver parenchyma. As was mentioned before, Thordarson has described such a decrease of prothrombin in some medicinal affections. Bechgaard in a 25 year old man who had just recovered from pneumonia found a prothrombin index of 50 (Lehmann's modification of Quick's method); after administration of vitamin K the prothrombin did not change but it rose spontaneously to normal in the course of 1 month. Begtrup and From Hansen report quite the same observation in a patient with erythema nodosum; in neither of these 2 cases there was any sign of liver disease. Constant or temporary refractory hypoprothrombinemia may thus, without any obvious cause, occur in a number of different affections. Further, as is evidenced by the two cases here reported, perfectly healthy individuals may present the same symptom. These facts must be kept in mind, when the ability of reaction to the administration of vitamin K shall be evaluated.

### Summary.

Persistent «idiopathic» hypoprothrombinemia, refractory to vitamin K, was observed in two healthy and otherwise normal adults. The occurrence of such an idiopathic hypoprothrombinemia must be kept in mind on judging the result of a prothrombin-liver function test.

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From Ullevål Hospital, Dept. IX. Norway. Internal medicine. Physician-in-charge Dr. O. Scheel.

## Atypical tuberculosis. — Boeck's sarcoid.<sup>1</sup>

By

ROALD OPSAHL.

(Submitted for publication September 28, 1942.)

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Tuberculosis is only etiologically a unit, and even then only to a certain degree. The various types of the tuberculous virus have by no means exactly the same biological properties. Even if only one of the known types of bacilli, the human strain is considered, it is known that, already in the specific morphological organ change caused by the bacillus, the differences begin to make themselves strongly felt. In the first place the exudative inflammatory changes, and in the second, the productive tumorous changes, are met with. There was a tendency earlier to try to draw a sharper line between these forms of tissue reaction. However, the conception has gradually been arrived at that these morphological differences are not due to anything but a different manner of reaction on the part of the organ cells, all according to the different sensitivity of these cells to the poison of the tubercle bacillus. And this sensitivity varies ex-

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<sup>1</sup> This article was written in 1939, but has not been previously published, because the author had hoped to have an opportunity to carry out a number of supplementary investigations to throw more light on one of the findings reported, the acid-fast granules which were proved in the specific granulation tissue in a case of Boeck's sarcoid (see p. 279).

Now, however, Schauman's and Hallberg's later work (see bibliography) has brought the question into a new position. It appears reasonable that the acid-fast granules which the present author proved and reproduced microphotographically (figs. 4 and 5) can be viewed in the same way as the «fungus elements» of Schaumann and Hallberg.

tremely, firstly from individual to individual, secondly from organ to organ, and finally from time to time in the same individual. In the great majority of cases there are both productive and exudative changes side by side. As one or the other form of tissue reaction becomes most pronounced, the process is called »productive» or »exudative» respectively.

Thus it will be the immune-biological conditions which are of decisive importance for the pathological organ changes, and accordingly also, to a material degree, for the clinical picture and course of the disease. As is well-known, a predominatingly productive manner of reaction with a tendency towards fibrous changes is associated with chronicity and clinical benignity, but on the other hand exudative changes are apt to constitute a more acute and, in clinical respects, malignant course.

As has been said, in the great majority of cases we find productive and exudative changes side by side, and corresponding clinical pictures which do not represent any extremes in one direction or the other. If we take for instance the most usual localisation, pulmonary tuberculosis, it must be said that every form, from and including caseous pneumonia on the one hand, through all the transition forms to and including chronic phthisis on the other, are all in themselves typical forms of pulmonary tuberculosis.

The question now is whether immune-biological or other factors can produce a manner of reaction which causes a case to fall outside the limits of the »typical», in the general sense of the word. Theoretically there are two possibilities. On the one hand, clinically there may be still more malignant and rapid forms than the pneumonic, forms in which perhaps the morphological organ changes have hardly developed before the organism breaks down. On the other hand, it is conceivable that there are special benignant forms with exclusively productive organ changes and particularly strong tendencies towards recovery. Let us see whether, in reality, there may also be cases which represent these extremes.

With regard to the first possibility, it might almost be thought that it must be very slight. Nevertheless, this kind of case, with what may be called a peracute course, is well-known. Such cases are described under various designations such as »typhobacillosis» or »sepsis tuberculosa acutissima». In this country Francis Harbitz and Bjarne Fretheim have described cases of this kind, Harbitz



*inter alia*, has described one by a designation which covers the essentials both in pathological-anatomical and in clinical respects: »Acute atypical miliary tuberculosis, i. e. without obvious macroscopical findings and making its appearance under the picture of lymphatic leukemia».

It is, however, the opposite extreme which plays the chief part both in practice and, above all, in theory, and it is on such cases I intend to dwell, on the so-called chronic miliary tuberculosis and related, or possibly identical conditions.

Already at a very early period the anatomists were aware that miliary tuberculosis might assume a chronic course, and also that it could possibly be cured. But it was not until after the assistance of roentgen examination was available that this question was successfully elucidated. Assmann was the first to show that miliary tuberculosis can be cured. This was in 1913. Considerable time elapsed, however, before it became clear that in reality this was no great rarity, as there was at first a tendency to believe. In the course of recent years a number of reports of such cases have appeared. In this country Stub and Holst Larsen published a survey of the question in 1932. In Sweden Hedvall has described a number of cases, and at the Pathological Congress in Oslo in 1935, Lindau dealt with the condition. During the discussion on that occasion, Harbitz stated that on going through his material he had come to the result that in reality the chronic miliary tuberculosis occurred twice as often as the acute. Finally, I will mention that, in a monograph published in 1927, Hoyle and Vaizey (England) gave a description of the disease based on 120 cases. They had themselves observed ten of these cases. The remainder they had collected from the literature, in that they had excluded 85 cases which had been published under that diagnosis, but where in their opinion there were not sufficient criteria to indicate that it was a question of tuberculosis.

The condition may occur at all ages, but is most frequently met with in the later years of adolescence and the earlier adult years. Previous clinical tuberculosis was proved in only a small number of the cases. At times the onset may be acute, but as a rule the illness develops insidiously with slightly pronounced lung symptoms, usually a dry cough or a cough with scanty sputum, and more or less obvious dyspnoea. As a rule there is no fever, and a physical examination of the lungs usually reveals nothing pathological. About one-

third of the patients had an enlarged spleen, general glandular swelling or tuberculous manifestations in other organs, especially the skin, urogenital tract, bones and joints. In strong contrast to the scanty or absent lung findings are the roentgen findings, which often reveal surprisingly severe changes. I shall not attempt here to enter more in detail into the roentgenological diagnosis and the various differential diagnostic possibilities, but only mention that screening is not sufficient. As a rule it is only with photography that the military shadow spots are discerned. They are generally small, discrete, and scattered symmetrically in both lung areas, as far as I know not infrequently chiefly in the apical area, while the basal parts may be clearer than normally. In barely half the cases only are tubercle bacilli found in the sputum. In the majority of the other cases the diagnosis is established histologically at biopsy or autopsy. Further, it is of the greatest interest to note that *among 39 cases in which the tuberculin tests were made, no less than 11 were tuberculin negative.* In 5 of these tuberculin negative individuals the diagnosis of tuberculosis was made histologically, and in 2 other tuberculin negative cases tubercle bacilli were found in the sputum. The authors point out that *decisive importance cannot be attached even to a negative Mantoux, which was found in 2 of the cases, as an obstacle to the diagnosis of tuberculosis.* The course of the disease varies greatly. According to the more or less pronounced chronicity, the authors divide their material into 3 groups, one with a subacute course (death within 6 months), one where death may not take place until after a period of more than 6 months and where there are often remissions lasting up to one year, and finally, a group where the development of the disease is arrested, and the patient is cured in the clinical and, later, possibly also in the anatomical sense. As the disease progresses it is seen roentgenologically how the military shadows gradually increase in size, lose their characteristic appearance, and further how, finally, there is confluence, and at times softening also. The border-line of ordinary pulmonary tuberculosis is then completely obliterated.

For the further consideration I intend to advance, the histological pictures shown by this form of tuberculosis are also of the greatest importance. What characterizes them particularly is the absence of necrosis, correspondingly few giant cells, pronounced fibrosis and slightly pronounced reactive lymphocyte infiltration.

Further, it is clear that diffusion takes place, firstly, along the blood channels, and secondly, along the lymph channels. In the latter case, which is comparatively rare, a reticular fibrosis appears in the lungs particularly, which is the cause of the characteristic changes shown by the roentgen picture in these cases.

*From what has been said above, it emerges that no sharp borderline whatever can be drawn between ordinary «classical» tuberculosis and chronic miliary tuberculosis. The transition is quite fluid both in clinical and pathological-anatomical respects. Let us now see what is met with if attempts are made to find definite distinguishing criteria between chronic miliary tuberculosis and Boeck's sarcoid, which is of the greatest interest at the present time.*

As is well-known, the morphological organic change first described by Boeck is the basis of a large number of different morbid pictures, in part fairly characteristic and previously known under names such as Besnier's lupus pernio, Jüngling's osteitis tuberculosa cystica, Heerfordt's febris uveoparotidea, etc. The merit of having proved that Boeck's sarcoid, or lupoid as he called it later, is met with in various other organs in addition to the skin may, as we know, be ascribed to Schaumann. We are particularly indebted to him for the knowledge of the localisation of the sarcoid in the lungs, tonsil, lymph nodes and spleen. Like Boeck himself and a number of later research workers with him, Schaumann is of the opinion that in reality it is a matter of a tuberculous illness caused by some strain of the tubercle bacillus. It has appeared to be a very difficult matter to prove this, however, and there are many who still hold the opinion that Boeck-Schaumann's disease cannot be apprehended as tuberculous, at all events not in every case. For that reason also, Schaumann's designation of the specific granulation tissue, lymphogranuloma benignum, has in many places become general in place of Boeck's sarcoid.

Now, as we know, the etiology of malignant lymphogranulomatosis is completely unknown. Common to it and to Schaumann's benignant lymphogranulomatosis would then be that both diseases are mostly localised in the main organs of the reticulo-endothelial system, above all in the lymph nodules, tonsils, spleen and liver. Now it has proved, however, that this is far from holding good. The Boeck changes are met with in all organs, and a systemic disease in the sense of Schaumann is not to be assumed. Further, it can

easily be realised that *histologically* Boeck's sarcoid has no resemblance to malignant lymphogranulomatosis. On the other hand, the resemblance to tuberculosis is so great that, on the whole, the two kinds of changes cannot be distinguished from each other. *In particular there is no distinction whatever between pronounced chronic miliary tuberculosis and Boeck's sarcoid.* Nevertheless the reason why there has been a disinclination to apprehend Boeck's sarcoid as tuberculous is that, as a rule, tuberculosis bacilli cannot be proved either by grafting or cultivation from the granulation tissue, nor as a rule has it been possible to find acid-fast bacilli in histological sections. Further, in this condition the tuberculin reaction is very often negative. This circumstance has resulted in the cases published with positive bacillus findings not having been accepted as cases of Boeck's sarcoid. Here, as so often otherwise, decisive weight has been attached to a negative finding. But in my opinion nothing is more erroneous, so much the more as it is known *that the tuberculin reaction is by no means always positive where it is provably a matter of tuberculosis.* In my discussion of chronic miliary tuberculosis I have only mentioned examples of this. No one has yet been able to give any definite explanation of why the tuberculin reaction fails in occasional cases. Possibly we are in the presence here of what Jadassohn has called positive anergy, a conception which I will not attempt to define more closely. But possibly also the explanation is to be sought in another circumstance, which Branch has suggested. He is of the opinion that it is the tuberculous necrosis alone which conditions the tuberculous allergy. This may in reality agree very well with our experiences. It is of course just the absence of necrosis which, above all, characterises both the most pronounced forms of benignant miliary tuberculosis and Boeck's sarcoid. I am of the opinion that there is good reason not to attach all too great importance to the negative result of the tuberculin tests. *At all events, it is not justifiable to draw far-reaching positive conclusions on the basis of such negative findings.* In reality this is of course what is done if one categorically denies the possibility that the absence of bacillus findings and negative tuberculin reactions can be consistent with a tuberculous etiology. This discloses a blind confidence in our methods and in our knowledge of allergy conditions in tuberculosis which is no compatible with a scientific way of thinking. Tubercle bacilli are in fact proved in occasional cases of Boeck's sarcoid

(Kyrle), and these few cases are in my opinion of equally great importance as proof material as all the others together. In any case it may be looked upon as quite unjustifiable to consider a positive bacillus finding a direct contradiction of the diagnosis of Boeck's sarcoid. This is to turn the matter completely upside down and to take up a preconceived attitude, whereby the whole firm foundation for the elucidation of the matter is shattered.

And this firm foundation is, as can be understood, none other than the morphological organ changes proved by Boeck in combination with the clinical characteristic feature of the disease. This characteristic feature is not based chiefly on the localisations of the changes, even though they may in themselves be typical enough and may condition all the syndromes I have already mentioned. It is seen that the changes may in reality occur anywhere, and that the possibilities of variations in the morbid picture are thus unlimited. The characteristic is based on one single thing, namely on its pronouncedly chronic course, in the tendency to fibrous changes and healing, exactly in the same way as is seen in the most pronounced chronic miliary tuberculosis, a condition which, to be quite frank, cannot in my opinion be distinguished on the whole from Boeck's sarcoid.

Basing myself on the previous survey I would draw the following conclusion: *It is at present impossible to draw any sharp line whatever between chronic miliary tuberculosis and ordinary «classical» tuberculosis on the one hand and Boeck's sarcoid on the other.* Anyone who states that he can do so draws positive conclusions on negative premises. It is another matter that anyone who acknowledges the absence of every tenable foundation for such a distinction will of necessity be strengthened in the belief that all these forms of disease are believed to have the same etiology. But for that reason he shall not be accused of having said that he knows that they are so.

I will now try to illustrate what I have said with some examples:

**Case 1.** 25-year-old student (A. L.) In 1932 and 1934 he is stated to have shown slightly positive tuberculin reactions; examined by a military doctor the first time, the second time by a medical student. (The strength of the reaction not indicated by figures).

At the end of March 1935 he fell ill. A week later he was admitted to the Med. Dept. A. at the State Hospital suffering from left-sided exudative pleurisy. He had fever, about 38.5 and a S. R. of 82 mm. The first Pirquet

blood pressure is said to have been high for perhaps 10 years, and she had often had nose bleedings.

At the beginning of October 1938 she had »bronchitis», and she coughed a great deal all through the autumn, with scanty sputum. Not febrile and no increased temperature when she measured it, which she has done when she has felt particularly listless (37.2—37.3 in the rectum in the evening). In the middle of January she consulted a doctor to get some »strengthening medicine». She was then Pirquet positive, had a raised S. R., and a roentgen picture taken by Dr T. E. Bentzen revealed definite indurations in both hilus regions radiating out from the hilus on both sides, atelectases basally in both lung areas, and small calcifications in the right lung base and lung apex. In the opinion of the roentgenologist the picture indicated bronchopneumonia.

On 17th February 1939 she was admitted to Ullevål, Dept. VIII, whose physician-in charge, Dr. Carl Müller, has been kind enough to allow me to describe the case. The patient was then in good condition and looked well. Temperature slightly subfebrile, S. R. 35 mm. Blood pressure 190/115, the heart slightly hypertrophic. Ecg. normal. A little crepitation at the left posterior chest downwards, otherwise normal physique. The liver probably considerably enlarged, there being a patch on the right side which went right down to crista ilei. The spleen slightly palpable 2—3 finger-breadths below the left costal arch. The urine physiological, and the kidney function normal. (Max. clearance 61.5 cm<sup>3</sup> per min.). In the blood there was a positive Takata-Ara reaction, negative Wassermann reaction; a plasma analysis showed 4 % albumins, 2.59 % globulins, 6.59 % total proteins, alb.-glob. quotient 1.54, Hgb. 85 %, red blood corpuscles 4.95 mill., white blood corp. 4,800 (of which 1.5 % eosinophils, 7.5 % staff nuclear, 63.5 % segment nuclear, 23.5 % lymphocytes and 4 % monocytes). Basal metabolism 107 %. At a roentgen examination of the thorax a slight hypertrophy of the heart was found, and with regard to the lungs the following: An old apex affection on the right side with calcified foci. In the perihilus fibrous irregular lines and slightly irregular indurations over the whole of the lower part of the right pulmonary area. »It has a rather strange appearance, somewhat resembling lymphangitis carcinomatosa, in any case resembling a stasis in the lymphatic vessels. There are probably enlarged glands in the right hilus. At the base and laterally a number of small, plate-shaped atelectases. On the left side some corresponding but less pronounced changes are present, especially in the hilus. At the base there are, on the left side also, flat shaped atelactases which are as pronounced as on the right side. Otherwise the left lung is clear.» (signed Frimann-Dahl). Bronchography reveals nothing pathological nor does urography. Secondary findings: gallstones, enlarged liver and spleen. The condition remained unchanged on the whole during her stay. She had no cough, her temperature remained subfebrile a long time and later became practically normal. For a time S. R. showed a tendency to rise and on 12/4 was 63 mm. In 5 measurings, after she had been 10 days in the department, her blood pressure was

normal. Further, it is of interest to note that at several examinations Rumpel-Leede's symptom proved to be present.

No certain diagnosis could be made on the basis of these findings. Something that readily suggested itself was a malignant granulomatosis. A test excision was made, however, of a lymph node about the size of a hazelnut which was found in the right supraclavicularis already on admission. At the histological examination made at the path. lab. (Dr H. Scheie) a strongly fibrous and partly calcified lymph node was found, in the outer layer of which there were seen typical tubercles of the chronic miliary type with scanty but distinct central necroses but few characteristic Langhans' giant cells, with sparse lymphocyte cells around their fibrous periphery.

With this the diagnosis was thus clear, and the whole morbid picture could be very easily understood. A chronic miliary tuberculosis was present, with hematogenic diffusion to various organs, in the first place to the lungs, possibly the hilus glands, throat glands, liver and spleen. It must be realised immediately that this illness very much resembles Boeck-Schaumann's disease. But nevertheless the diagnosis chronic miliary tuberculosis must be made on account of the histological finding, which is not identical with that described by Boeck, even though it is midway between the latter and what is found in ordinary tuberculosis.

**Case 3.** The third case I shall refer to is still closer to Boeck-Schaumann's disease, so close that it is impossible to say where it should be placed:

A 29-year-old woman from a healthy family. During her first pregnancy, when she was 18 years old, she had an attack of kidney trouble. Otherwise she had previously been healthy on the whole. On 27/6 1938, after having had a chill for a couple of weeks, with a severe cold in the head but without any cough or sore throat, she developed some bluish-red, slightly raised, tender nodules from the knee-joints down over the fronts of both legs to the ankles. At the same time she had pains in the knee-and ankle-joints and alternate fits of shivering and sweating. She was up for a week and then stayed in bed for about 1—1 ½ weeks. The tender spots had then disappeared. After she got up, an eruption of the same kind of nodules appeared again on the lower extremities, and in addition one single one in the right elbow region. The local doctor then took a Pirquet test with negative result. S. R. probably slightly increased. On 25/7—38 she was admitted to Ullevål Hospital, Dept. IX, under the diagnosis erythema nodosum. She was then in good condition and looked well. Afebrile, S. R. 62 mm. On the front of left crus a single reddish coloured, slightly infiltrated, tender spot. No symptoms in the joints, no glandular swellings. Nothing provable at a routine examination of the thorax and abdomen. Ecg. normal. Urine physiological. Meinicke Clarification test II ÷ in the blood. White blood



Fig. 1. Case 3. Specific skin eruption on the throat.

corpuscles 7,800, normal blood picture. At the first examination Pirquet was negative, or in any case not definitely positive, 9—2 mm. At the next examination immediately afterward slightly positive 7—3 mm. At the same time Mantoux positiv (1 mg 40—25 mm.) On roentgen examination of the thorax the lungs were clear. Left hilus large and dense with laterally convex contours. Upwards posteriorly a faint shadow the size of a hazel-nut is seen, best visible on the lateral picture. Diagnosis: Adenitis hili sin. (signed Poulsson). The patient remained in the dept. nearly 5 months, the whole time confined to bed. She was consistently febrile-slightly subfebrile, had a constantly considerably raised S. R., the first part of the time with a falling tendency down to 30 mm, later rising again to a maximum of 96 mm, at the last examination 78 mm. Her weight exhibited a number of variations, but at the time of her discharge had increased by 4 kg since her



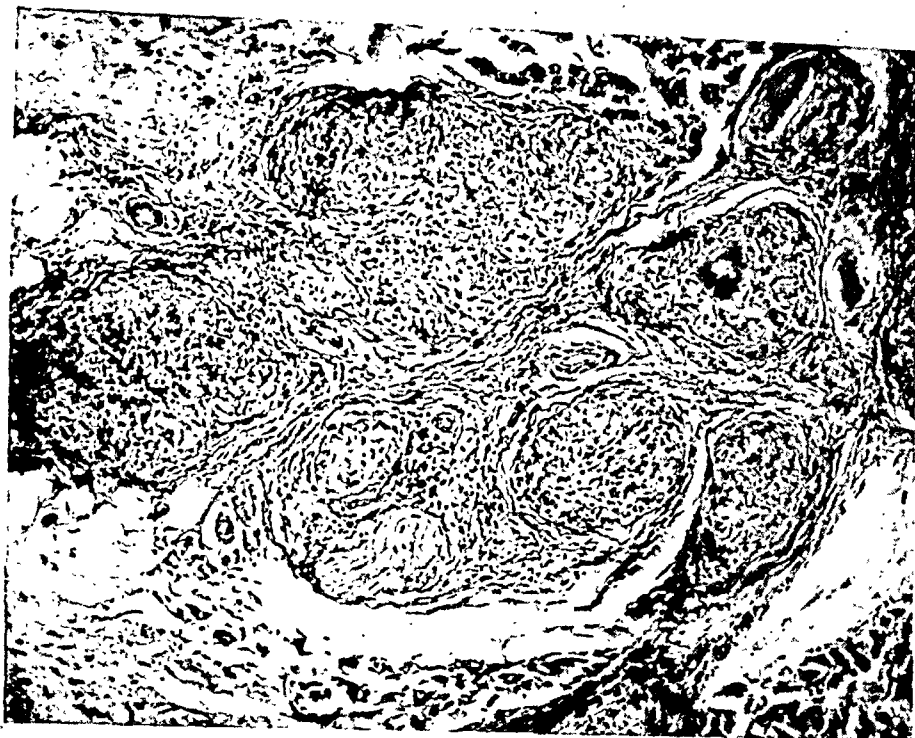


Fig. 2. Case 3. Histological section of the specific skin eruption. Enlarged 100 times.

admission. No cough. What was striking, however, was that her eruption, which otherwise developed like a typical erythema nodosum with scanty efflorescences, appeared and disappeared at short intervals during her whole stay. It was localised chiefly in the lower extremities, principally in the crura, but also in the femora, and occasionally also in the hands and arms. At the same time she often complained of pain in the joints. Examinations of the white blood corpuscles were made several times, when increasing monocytosis was found — the last time 12 % — otherwise no essential change from the first examination. Towards the end of the stay a plasma analysis was made, 5.84 % total protein and an A/G quotient of 1.18 being found. The ventricle irrigation fluid was cultivated for TB and inoculated on guinea-pigs with neg. results. Ordinary blood cultures were also made with negative result. Of the greatest interest were, however, the control examinations of the lungs and the results of the tuberculin tests. A month after the first examination it was found that the induration in the left hilus had increased somewhat. Further small shadow spots on the right side laterally in the 1st and 2nd intercostal spaces were met with. After about another month an unchanged picture, and another after 6 weeks. At the last control on 8/12—38 it was found that the small infiltrations in the right apex extended towards the hilus, not very dense and not sharply delimited. But there were also now, principally on the right side,

fairly small miliary foci, which aroused suspicions of an extension, (Frimann-Dahl). The tuberculin reaction, which had been slightly positive at admission, was tested 6 times later and exhibited considerable variations: Pirquet 13th August 20—6 mm, 26th Nov. 3—1 mm, Dec. 1—0 mm, 16th Dec. 8—2 mm and Mantoux at the same time 30—15.

Not unreasonably the patience of this patient was very severely tried by this long stay in bed, and when 5 months had passed we allowed her to go home after the eruption had disappeared for a time. She had been allowed to be up for some days and felt fairly well.

On 16th March 1939, nearly three months after her discharge, she came for out-patient control, sent by the doctor in her town. She had been well, however, and her S. R. had fallen to 19 mm.

I noticed a peculiar small papular eruption on the patient's face and neck which, according to her own statement, had just begun to appear shortly before her discharge from the department. In my opinion the eruption had a specific character, but the skin doctor (Dr Lars Hannisdahl), who kindly looked at it for me, dared not make any definite diagnosis. He recommended a test excision which we hesitated to make. However, I had a number of photographs of it taken (fig. I), and also had a test excision made, a small group of papules being found on the front of the thorax. In this way I was able to get my diagnosis confirmed. In a section from this little piece of skin (fig. II) there is a granulation tissue which corresponds fairly closely with that found in Boeck's sarcoid. However, there is an indication of necrosis centrally in occasional miliary nodes and corresponding to them occasional giant cells. So as far as that is concerned, it may equally well be characterized histologically as tuberculosis. If one refuses to apprehend these skin efflorescences as Boeck's sarcoid, one must probably designate them papulonecrotic tuberculides. Nor after all is there perhaps any sharp border-line between these forms of skin tuberculosis. In any case the result of the last roentgen control examination of the lungs, which I now had reason to make, argues fairly strongly in the direction of Boeck's sarcoid, although the skin efflorescences have much in common with papulonecrotic tuberculides. The roentgenologist gives the following description of the sciagram taken on 18th March: The condition is approximately the same as at the former examination. However, it is seen more clearly now than then that in the right lung there are scattered miliary and submiliary foci, densest in the upper lobe, from which they spread fanwise over towards the hilus, where there is probably a slight glandular swelling. On the left side there is an undoubted glandular swelling in the hilus, a tumour fully the size of a walnut. On the left side also there are obvious submiliary foci, both in the top area and down across towards the diaphragm. The changes agree well with Boeck's sarcoid (signed Frimann-Dahl).

**Case 4.** Finally I will describe a fourth case, one in every respect typical of what the French, (Pautrier,) characterize as «forme gangliopulmonaire» of Boeck-Schaumann's disease. This patient does not differ

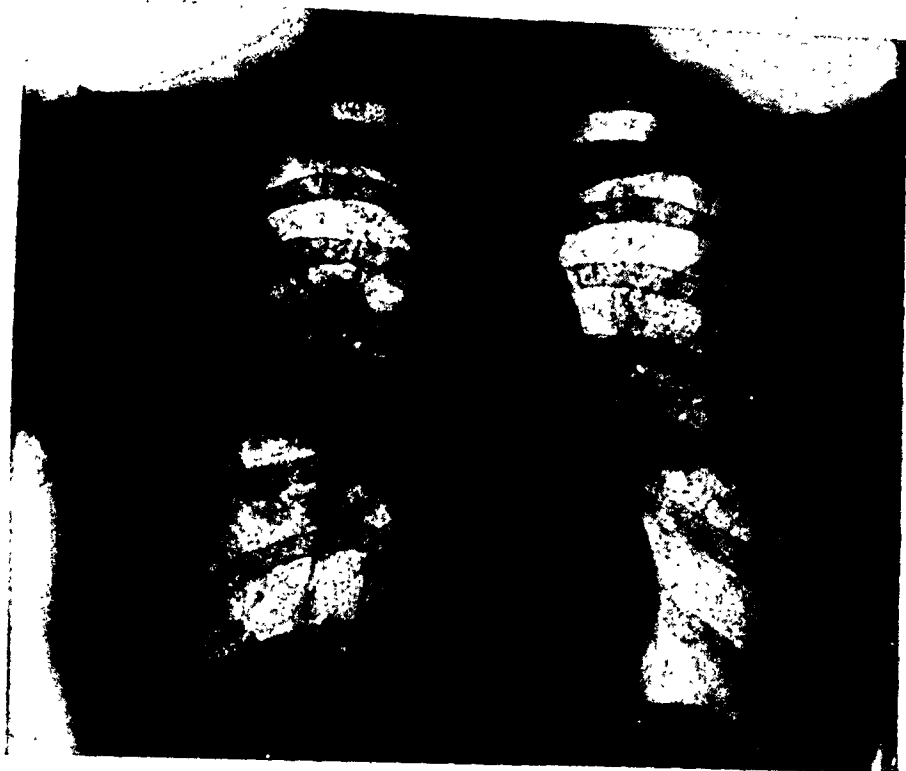


Fig. 3. Case 4. Roentgen photograph of the thorax 2/2—39. Typical Boeck's sarcoid in the lungs.

from the preceding case, except that both the gland affection and the lung affection are more pronounced, at the same time as the tuberculin reaction is completely negative. In other words, we have arrived at what I think can probably be apprehended as the extreme form of chronic miliary tuberculosis.

It is the case of a 45-year-old woman (A. Ö.). About the mother we have the interesting information that she suffered from lupus nasi, (died of pneumonia). In June 1938 the patient noticed the first signs of her illness, a feeling of tightness in the throat, dyspnoea on stairs, no cough but troubled by mucus in the nose and throat, at times nose-bleeding. In the late autumn she felt particularly limp and weak for a couple of periods and had attacks of heat but not shivering fits. The times she took her temperature it proved to be normal. On December 1st she was examined by Dr O. Scheel who proved increased S. R. (35 mm) and glandular swellings in both supraclavicular cavities. Pirquet: negative (1—1 mm.). Roentgen examination made the next day by Prof. T. Dale revealed the following: »The lungs exhibit a strange picture with pronounced striae which run from the hilus over towards the thorax almost horizontally on both sides. On the lateral pictures the striae are seen to run chiefly forwards. In addition to

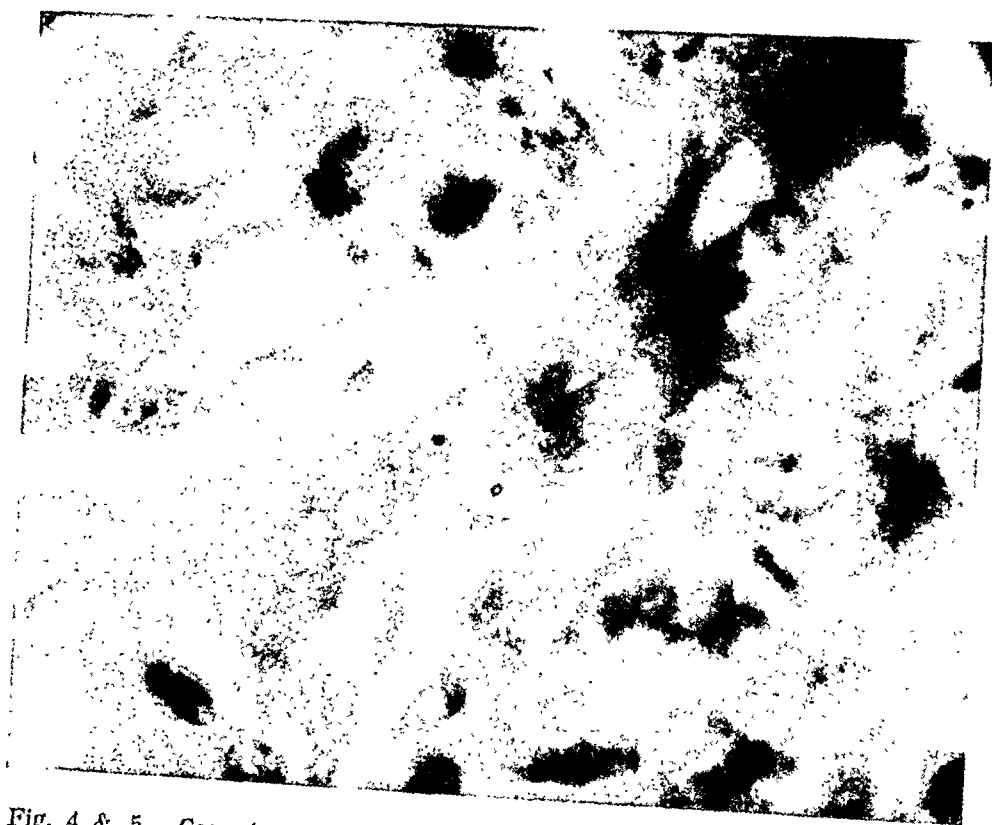
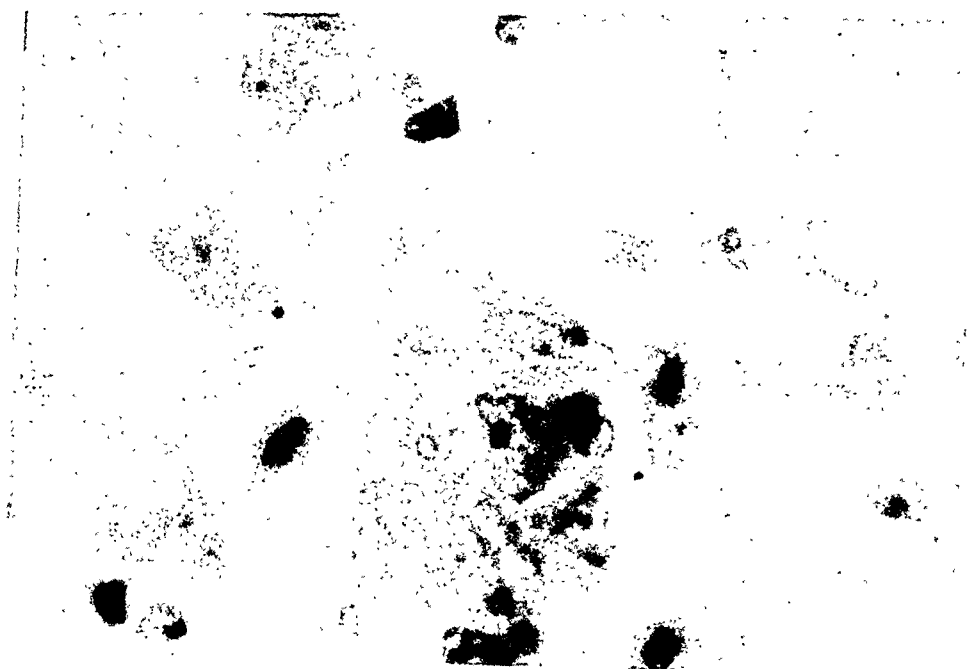


Fig. 4 & 5. Case 4. Acid-fast granules in histological sections from the specific granulation tissue in the lymph nodes. Enlarged 1500 times.

these striae dense patches of shadow are seen symmetrically distributed over both lung areas around hilus, extending upwards towards the clavicle and downwards towards the diaphragm medially. The hilus area is difficult to appraise. It looks as though the hilus is pressed somewhat outwards owing to the above-mentioned striae, which may represent fibrous changes. It is possible that there are indurations on both sides in the hilus. No cavity can be found. The diaphragm moves well, and the sinus is free on both sides. Over the right apex there is a slight pleural thickening. If there had been a more obvious glandular swelling in the hilus, and there had not been the fibrous tension, one's first thought would have been Boeck's sarcoid. Nevertheless, it is possible that that condition is present. The symmetrical diffusion might argue in its favour. The fibrous changes might argue more in the direction of a tuberculous process, but then it is remarkable that the changes should be so symmetrical. On 6/1—39, when the patient was admitted to Ullevål, Dept. IX, she was in good condition. Respiration was untroubled and she had no cough, was afebrile, but had a S. R. of 66 mm. In the right fossa supraclavicularis 2 firm lymph nodules the size of hazelnuts were felt, in the left one nodule. Physically she was normal, and over the abdomen there was nothing pathological, in particular no enlargement of the liver or spleen. Urine physiological. The tuberculin reaction was still negative, and on roentgen examination of the lungs the same picture as was described before was revealed, to which Dr Frimann-Dahl gave about the same interpretation as Prof. Dale. Roentgen examination of the skeleton of her hands and feet revealed nothing pathological. At the further blood examinations there was a very slight secondary anemia, a normal number of white blood corpuscles, 5.5 % of which were monocytes and 6.5 % eosinophiles. Seroreactions for lues were negative (Meinicke Clarification test II and WR). There was nothing particular to be noted about the condition of the plasma proteins. Ecg. normal. She was also examined in the special departments with a view to possible eye changes and changes in the nose and throat, but without anything abnormal being found. Finally, she was examined by a skin specialist, who found on her left upper arm an efflorescence the size of a hemp seed, which in his opinion consisted of 2—3 miliary nodes of specific nature. To obtain a closer diagnosis a total of 6 lymph nodes, ranging in size from peas to Spanish nuts, were examined from the right f. supraclavicularis. Histological examination at the pathological laboratory of these glands, which were firm with a homogenous, greyish-red section surface (Dr Ebbe Thorgersen), revealed the following: They are scanty remains of the original lymphoid substance. For the rest the glands consist of a peculiar pathological tissue, which forms dense round nodes built up of epithelial cells. In no place is there central necrosis. Quite a number of giant cells of Langhans' type are to be seen, but also nuclear ones scattered about in the cytoplasm. The nodes are delimited from each other by richly developed fibrillar connective tissue. This connective tissue also encircles the individual nodes. D.: a strange fibrous form of tuberculosis. TB not to be found.

To obtain bacteriological proof, if possible, that it really was a matter of tuberculosis, we cultivated this crushed granulation tissue and stirred it up to a gruel with sterile salt water. This material was inoculated both on adult guinea-pigs and on undeveloped animals. One of these animals died some weeks later from a kidney disease which was not of a tuberculous nature. The others were killed after a full year and showed no tuberculosis. Without going closer into detail, I will only mention further that a number of other examinations were made to find, if possible, tubercle bacilli in this patient. Cultures were made from the granulation tissue (prosector E. Wåler) but with ordinary sulphuric acid treatment and on the usual substratum with negative results. Further I examined the patient's blood by inoculation on a number of young and full-grown guinea-pigs, on rabbits and on fowls, all with negative results. Cultivation on ordinary medium, but without sulphuric acid treatment, also gave negative results. Unfortunately no cultivation on Petraghani's substratum was made either from the blood or the extirpated glands, nor were the latter inoculated on rabbits. If this had been done, the chances of finding TB would possibly have been greater.

With regard to the patient's condition during her further stay in hospital, which lasted a full month, it may be said: As a rule she was subfebrile, coughed occasionally with scanty sputum (which was also inoculated on guinea pigs with negative results). Stayed in bed and appeared to benefit from it, felt stronger when she got up after about a month. A number of tuberculin tests were made successively, partly with ordinary tuberculin and partly with chicken tuberculin, negative results being consistently obtained both from Pirquet and Mantoux tests. Towards the end of her stay she was inoculated with BCG ad mod. Lemming to find, if possible, support for so-called positive anergy similar to that which the author mentioned thinks that he found in another case. She received an ordinary dose (0.01 mg), after which a subcutaneous infiltration the size of a pea appeared. At a control examination on 3/3 this could still be felt. Pirquet had then become positive, 10—3 mm. Lemming did not obtain a local reaction until after a treble dose, and the tuberculin reaction was still negative. So this condition probably varies. Further, a couple of control pictures of the lungs were taken on 2/2 (Fig. III) and 17/4—39. These showed that the infiltration in the lungs gradually increased somewhat, and the hilus contours on these pictures are so indistinct that it could not be determined whether there was a glandular swelling. After the later examination Dr Frimann-Dahl pointed out, further, that the infiltration is situated chiefly in the medial and anterior part of the upper lobes, while both the posterior part of the upper lobe and the lower lobes on both sides are free. (This circumstance plays a certain differential diagnostic rôle, namely against silicosis, in which the infiltration is situated particularly in the upper lobe posteriorly downwards or in the lower lobe posteriorly upwards). The roentgenologist then unreservedly made the diagnosis Boeck's sarcoid, which is in complete agreement with the result of the histological examination of the lymph nodes. Together with the clinical finding, this finding provides an absolutely definite foundation for the diagnosis.

As has been mentioned previously, TB was not found at the first histological examination of the extirpated glands.

Since, however, as has been mentioned, it may be very difficult, even in cases of ordinary chronic miliary tuberculosis, to establish virus in histological preparations, the investigation was continued on this point. Although a large series of sections from different glands was examined as thoroughly as possible, no acid-fast staff cells could be proved either. On the other hand, careful examination with c. 1500 times' enlargement revealed, scattered almost everywhere in the epithelial tissue, very small, acid-fast, shiny red, round or oval bodies, which I was at first most inclined to apprehend as transverse sections of acid-fast staffs. By degrees, however, as there were still more of these round bodies just in the places in the sections where virus might be expected, in epithelial cell tubercles and never in the tissue between them, I became convinced that it was not a question either of transverse sections of staff cells or of artefacts, but of round, *acid-fast granules* (Figs. IV and V). What significance is to be attached to these granules is another question which will not be dealt with here.<sup>1</sup>

### Summary.

In a brief survey the author endeavours to demonstrate the indefinite transitions both in clinical and in pathological-anatomical respects between the different expressions of tuberculosis, from the «atypical» peracute tuberculous sepsis on the one hand, to the ordinary exudative and productive forms of tuberculosis respectively, to the «atypical» chronic miliary tuberculosis on the other. Further, the same indefinite transition is proved both in clinical and in pathological respects between chronic miliary tuberculosis and Boeck's sarcoid, which, in the author's opinion, in all probability represents the extreme form of chronic miliary tuberculosis, although at present this has not been proved. In the ordinary chronic miliary tuberculosis positive bacillus findings and positive tuberculin reaction are the rule, while negative bacillus findings and negative tuberculin reactions are the exception. In the case of Boeck's sarcoid the conditions are reversed. But in both groups the

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<sup>1</sup> See footnote on p. 267.

exceptions are so numerous that the designations chronic miliary tuberculosis and Boeck's sarcoid respectively cannot be based on these criteria. Boeck's sarcoid (or lupoid, as Boeck also called it) should, in the opinion of the present author, be apprehended as an anatomical and not a clinical conception. Clinical conceptions are Besnier's lupus pernio, Jüngling's osteitis tub. cystica, Heerfordt's febris uveoparotidea and Schaumann's disease, which all have one thing in common, namely the pathological-anatomical substrate described by Boeck. The author endeavours to illustrate with examples these indefinite transitions, firstly from case to case, and secondly in the individual case where the change in the immunobiological conditions are assumed to coincide with proved changes in the tuberculous allergy accompanied by corresponding changes in the clinical picture of the disease. (Case 3).

Finally, the author states that in histological sections of the specific granulation tissue (lymph nodes) from a typical case of Boeck-Schaumann's disease he has proved acid-fast granules. (figs. IV and V).

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From the Medical Clinic (Director: Professor Sven Ingvar) of the Royal University at Lund (Sweden).

## The occurrence of thrombosis and pulmonary embolism in pneumonia.

By

ERIK ASK-UPMARK, M.D.

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The occurrence of venous thrombosis and pulmonary embolism in connection with disorders belonging to the internal medicine has been well established during recent years. It has even been maintained that the incidence of fatal pulmonary embolism should be greater in internal diseases than after surgical interventions (for references see Geissendörfer 1935 and Hultquist 1936). Nevertheless, there is a striking disproportion between the numerous surgical investigations dealing with this much dreaded complication and the comparatively feeble interest devoted to the matter by internal authors. The reasons for this difference may be variable but one of them is doubtless the fact that whereas thrombosis and pulmonary embolism, appearing in connection with an operation, may be ascribed to a definitely timed traumatic incidence, the surgical intervention, difficulties in this regard do arise when most internal disorders are about. If, for example, a venous thrombosis should occur during the course of a pulmonary tuberculosis or a valvular lesion of the heart, the chronic nature of these conditions makes it difficult or impossible to attempt an explanation why the thrombosis should have occurred just at that very moment of the sequence of events. There are, as a matter of fact, only few internal disorders, complicated by thrombosis-embolism (TE), where it seems

possible to obtain a definite time table between the primary pathological lesion and the secondary appearance of the complication in question. Such disorders are lobar pneumonia, coronary thrombosis and certain instances of pernicious anemia (cases not previously treated, where the onset of the treatment may be selected as the start point of the itinerary). The occurrence of TE in connection with lobar pneumonia represents a well established issue (cfr. for example Reimann 1938 and Ingvar 1939). The present study will attempt an analysis of this occurrence of TE in pneumonia with special regard to the chronological point of view. Investigations dealing with the same matter in coronary thrombosis are to be published in another communication.

### *Material.*

The material was represented by 1454 cases of lobar pneumonia, observed in the clinic during the years 1916—1941. In this material venous thrombosis or (and) pulmonary embolism (TE) was registered in 27 instances, making a percentage of 1.9 %. In about every 50th case of lobar pneumonia TE was hence to be observed.

Table 1. Sex and age.

|        |                  | All instances | < 40 years | ≥ 40 years |
|--------|------------------|---------------|------------|------------|
| Male   | pneumonias ..... | 979           | 578        | 401        |
|        | TE .....         | 11            | 5          | 6          |
| Female | pneumonias ..... | 475           | 203        | 272        |
|        | TE .....         | 16            | 6          | 10         |

It will be seen that the percentage of TE in pneumonia was in males about 1.1 %, in females 3.4 %. If the various ages are considered the percentage will become: —

|                     | < 40 years | > 40 years |
|---------------------|------------|------------|
| in both sexes ..... | 1.4 %      | 2.2 %      |
| in males .....      | 0.9 %      | 1.5 %      |
| in females .....    | 3 %        | 3.7 %      |

Although no undue importance should be applied to these figures on account of the limited size of the available material it may be presumed that TE is more frequent among older than among

younger persons afflicted with lobar pneumonia and more common in females than in males. This incidence is in accordance with the general experience on the occurrence of TE after surgical operations. A more detailed review of the various observations will be found in the following table.

Table 2. Sex and age of TE.

| Age   | Men | Women |
|-------|-----|-------|
| 10—19 | 2   | —     |
| 20—29 | 2   | 2     |
| 30—39 | 1   | 3     |
| 40—49 | 3   | 3     |
| 50—59 | 3   | 5     |
| 60—69 | —   | 1     |
| 70—79 | —   | 1     |

The youngest man was 17, the oldest 57. The youngest woman was 26, the oldest 70. In most instances the primary manifestation of the TE was represented by venous thrombosis but in 8 cases pulmonary embolism was the first lesion to be observed (in 4 males, aged 17, 21, 43 and 49 and in 4 females, aged 27, 56, 66 and 70, the embolism becoming fatal in two men, aged 43 and 49 and one woman, aged 66).

With regard to the frequency of TE in the various years concerned by the material the following table will be a brief summary.

Table 3. Incidence in various years of TE.

|           |    |                                       |
|-----------|----|---------------------------------------|
| 1916—1920 | 1  | (male)                                |
| 1921—1925 | 3  | (1 male, 2 females)                   |
| 1926—1930 | 5  | (3 males, 2 females)                  |
| 1931—1935 | 2  | (1 male, 1 female, last case 1932)    |
| 1936—1940 | 13 | (4 males, 9 females, first case 1938) |
| 1941      | 3  | (1 male, 2 females)                   |

It should be observed that during the last 4 years (1938—41) more (16) instances of TE have been taken to the records than during the preceding 22 years (1916—1937: 11 cases). The most outstanding cause for this remarkable fact seems to be the introduction of specific therapy, by means of which instances have been brought to survive, who otherwise might have succumbed before their having the opportunity to develop TE. Thus, in

1938—1941 there are 16 TE in 353 pneumonias = 4.5 %;  
 1916—1937 » » 11 TE » 1101 » = 1 %.

Specific treatment (serum, chemotherapy or both of them) was applied to 12 out of the 16 instances of TE observed since 1938; it was applied to none of the 11 cases previously observed. It might, on the other hand, be surmised that the apparent increase of TE in the pneumonias during the last 4 years be due to an alteration of the material with regard to the age or the sex of the patients afflicted with pneumonia. That such cannot be the case will be seen from the following considerations.

|                   | All pneumonias | Pneumonias < 40 years |
|-------------------|----------------|-----------------------|
| Before 1938 ..... | 1101           | 499                   |
| 1938—1941 .....   | 353            | 182                   |
|                   | All pneumonias | Females               |
| Before 1938 ..... | 1101           | 346                   |
| 1938—1941 .....   | 353            | 129                   |

The percentage of aged and of women, i. e. of the groups according to table (1) and (2) most severely affected by TE, is obviously the same during the two periods here concerned. On the other hand the percentage of aged survivors has most certainly increased during the recent period on account of the introduction of specific treatment; and this seems to be the main reason for the increased percentage of TE in the material since 1938. The question may be raised whether not the specific therapy in itself may favour the development of TE. An apparent support for this view may be derived from the fact that before 1938 there were 599 pneumonias of less than 40 years of age, including 6 TE (= 1 %), whilst 1938—1941 there were 182 pneumonias below 40 years including 5 TE (= 2.7 %). But on the one hand the difference is not significant from statistical point of view, and on the other hand a scrutinizing of the primary material will show that in 1938 not all instances were treated with specific therapy: among the 5 TE below 40 years there were thus 2 who did not enjoy the treatment in question! Considering this evidence it cannot justly be maintained that the specific therapy has increased the occurrence of TE in pneumonias otherwise than indirectly, by augmenting the number of survivors; it has, on the other hand, not reduced the incidence here discussed.

The number of days elapsed between the onset, viz. the crisis of pneumonia and the clinical onset of the TE, was a subject of particular interest. In some few instances the details about the onset and the course of the illness were less complete and in others the occurrence of irregular features such as migrating pneumonias was liable to obscure the time-table so that only 20 instances out of the 27 were to be used. In 6 out of these 20 instances there was a lysis instead of a crisis. The observations will be seen in the following table:

**Table 4. Clinical onset of TE in pneumonia.**

Days after onset of the pneumonia (20 cases): 8—21, on an average 13.4 days  
 \* \* crisis \* \* \* (14 cases), 4—12, on an average 8 days.

| Case | Sex, age | Record  | Days after onset | Days after crisis | First symptom | Specific treatment  |
|------|----------|---------|------------------|-------------------|---------------|---------------------|
| 1    | M 43     | 79/16   | 20               | 11                | E †           | No                  |
| 2    | F 53     | 677/22  | 21               | 12                | T             | No                  |
| 3    | F 33     | 136/23  | 19               | 12                | T             | No                  |
| 4    | M 51     | 1251/28 | 16               | 10                | T             | No                  |
| 5    | M 30     | 364/29  | 14               | 7                 | T             | No                  |
| 6    | F 66     | 667/29  | 14               | 8                 | E †           | No                  |
| 7    | F 35     | 2457/31 | 13               | Lysis             | T             | No                  |
| 8    | M 17     | 1625/32 | 10               | 4                 | E             | No                  |
| 9    | F 51     | /38     | 13               | Lysis             | T             | No                  |
| 10   | F 31     | 304/38  | 11               | Lysis             | T             | No                  |
| 11   | M 21     | 670/38  | 12               | 5                 | E             | No                  |
| 12   | F 56     | 1429/38 | 14               | Lysis             | E             | Yes, S <sup>1</sup> |
| 13   | F 38     | 522/39  | 18               | 8                 | T             | Yes, S. Ch.         |
| 14   | M 49     | 572/39  | 9                | 7                 | E †           | Yes, Ch.            |
| 15   | F 42     | 809/39  | 8                | 7                 | T             | Yes, S.             |
| 16   | F 47     | 2742/39 | 14               | 6                 | T             | Yes, Ch.            |
| 17   | M 47     | 3020/40 | 11               | Lysis             | T             | Yes, Ch.            |
| 18   | F 52     | 701/40  | 10               | 2                 | T             | Yes, Ch.            |
| 19   | F 27     | 2501/41 | 8                | 7                 | E             | Yes, Ch.            |
| 20   | M 57     | 951/41  | 14               | Lysis             | T             | Yes, Ch.            |

<sup>1</sup> S = Serum, Ch. = Chemotherapy.

<sup>2</sup> In this case the T occurred 10 days after onset of the pneumonia but before the apparently postponed crisis.

It will be seen from the table that the first symptom in most instances was represented by T, only in 6 cases by E. As with the postoperative TE it was found that if T was the first symptom it

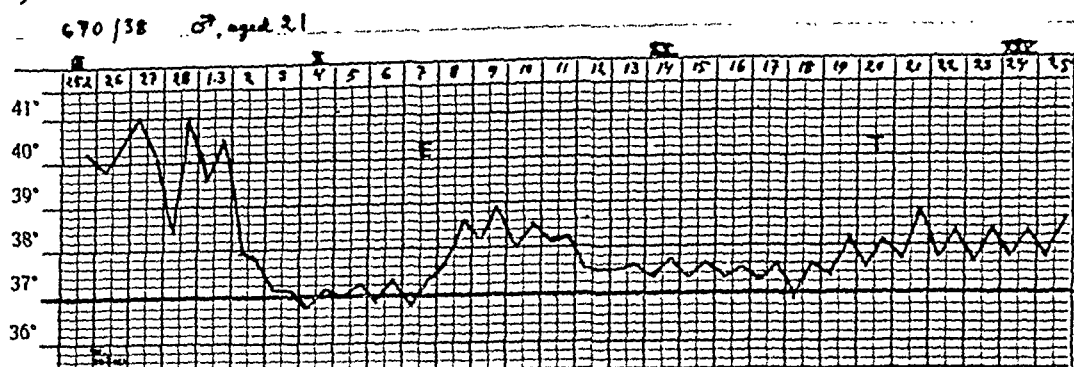
was rare for any E to occur (such was the case only in case 15, where the T antedated the E by one day), whereas if E was the first symptom and the patient did survive a T did appear sooner or later (cases 8, 11, 19). With regard to the clinical diagnosis of T viz. E it was performed along the usual lines with the reservation that only local symptoms were considered conclusive (T: pains in the calf, tenderness below the anterior end of calcaneus or in the deep structures of the calf, oedema, heat and cyanosis; E suddenly appearing pleural pain in the chest, followed by the characteristic bloody (not rust-brown) sputum and eventually by T or by death and autopsy). This restriction on the one hand, the fact that an elevated temperature or pulse often did precede the onset of TE on the other make it obvious that the average time elapsed between the onset of pneumonia and the onset of TE rather should be considered as shorter than the time here indicated, 13.4 days. It was however not possible to utilize the behaviour of the temperature in order to determine the onset of TE since it was found that in the very majority of the cases here concerned the temperature did not reach the normal level between the crisis (or lysis) and the onset of TE, such being the case only in the observations (4), (8), (11) and possibly also (1), and neither was the pulse of conclusive character.

From practical clinical point of view the conclusion seems warranted that the evolution of TE is particularly to be feared in such instances of lobar pneumonia, where the temperature does not attain the normal level in connection with the crisis or the lysis, although it may occur also if this level is reached. It was also observed that in some instances [(17), (20) and in a case here not tabled of a woman, aged 26] the pneumonia was to be considered as a recurrence, but since recurrences anyway do occur to a certain extent in lobar pneumonia no conclusions seem to be allowed from this observation. In two instances serum sickness was noted (case 15 and one case not here tabled of a woman aged 52); it did not occur at the same time as the TE (in case 15 seven days after the TE, in the other case five days prior to the TE). In at least two instances [cases (17) and (20)] typical rashes, induced by the chemotherapy, were present when the TE did appear; the limited size of the material makes it impossible to decide whether this represents a mere accidental coincidence (cfr below).

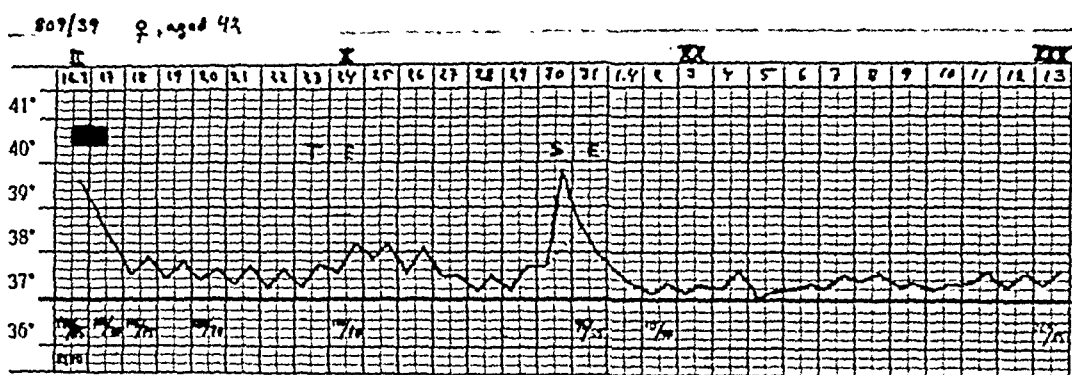
*Comment and discussion.*

When attempting to date the occurrence of TE induced by a surgical intervention it is possible to get a fix starting point for the sequence of events, as represented by the operation. When the occurrence of TE in lobar pneumonia is about we have from this point of view the advantage of a sudden onset of the disease, often also of an abrupt crisis. It is true that the classical duration of a pneumonia amounts to one week, whereas the operation is performed in hours, but this difference should not be overemphasized since the tissue injuries established by an operation will not be healed at the moment when the operation is finished. It has been established beyond doubt that the majority of postoperative TE is to be expected during the second week after the operation, the maximum on an average being reached on the 10th day. The evidence brought forward in the present investigation will apparently represent a most interesting parallel to this phenomenon, since it has been demonstrated that the average time elapsed between the onset of the disease and the onset of TE was about 13 days. For reasons already indicated it may be presumed that this interval is, in reality, not quite so long. If on the other hand the period is considered elapsing between the crisis and the onset of TE this period was found to average 8 days, or possibly some day less if the source of error contained in the general symptoms (temperature etc.) is to be considered. The question may be raised whether the dices of fate with regard to TE have been thrown with the onset, with the course or with the crisis of the pneumonia. Since TE occasionally may be observed to occur before the onset of the crisis and since it may be met with else in cases finished with lysis the crisis in itself seems to be of less importance, although the resolution of the pneumonia with its absorption of large amounts of organic matter cannot reasonably be discarded in this connection. Most probably the whole sequence of events induced by the lobar pneumonia during its course is to be held responsible for the development of TE; with regard, however, to the desirability to obtain a fixed date with which to work it seems logical to reckon with the onset of the pneumonia. If this is done we will obtain 13.4 days or somewhat less, say 11–12 days as the average period of time necessitated for the evolution of TE in its clinical sense. Another possibility, perhaps more ade-

) a)



b)



Temperature curves in four instances of lobar pneumonia

Symbols E: pulmonary embolism

T: Trombosis

S: Serum-reaction

Roman figures: days of pneumonia (I onset)

■ : Seruntreatment

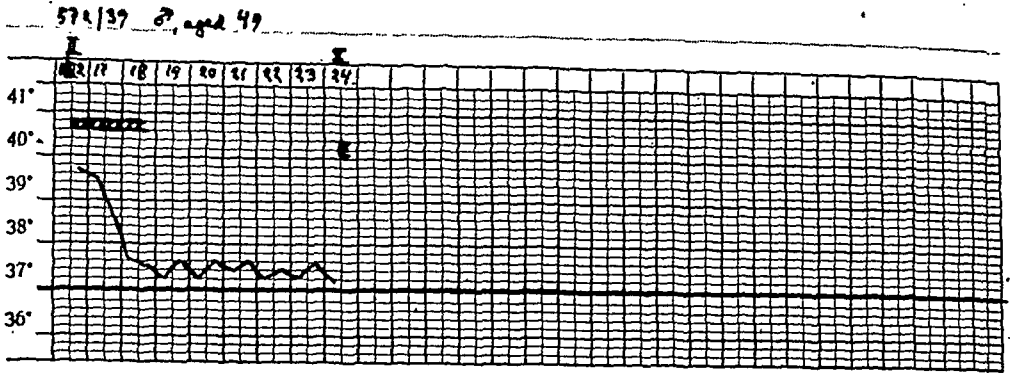
▨ : Chemotherapy

quate but a bit more awkward, would be to reckon with the middle day of the pneumonia as the starting point; in this case we may obtain a TE on an average of 9—10 days after this date, i. e. at exactly the same time as after a surgical intervention. It may be added that in as much as specific therapy is being used at an early stage of the pneumonia the duration of the disease will become accordingly abbreviated, so that the deductions here necessitated may be avoided; it is instructive to note that in those very cases of the present material (14, 15, 19) where the duration of the disease did not exceed 2 days the pulmonary embolism did appear already 8—9 days after the onset of the pneumonia.

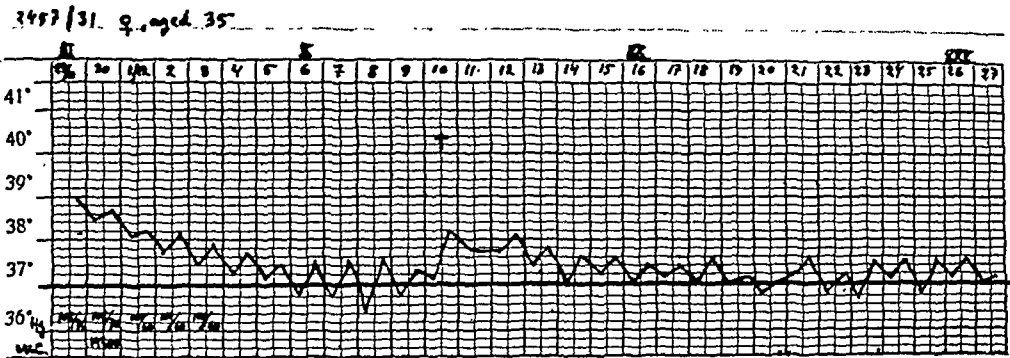
The striking similarity hence ascertained between the occurrence of TE after operations and after pneumonia makes it reasonable



D 9



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Temperature curves in four instances of lobar pneumonia

Symbols E: pulmonary embolism

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S: Serum-reaction

Roman figures: days of pneumonia (I onset)

— : Serumentreatment

/// : Chemotherapy

to presume a common pathogenesis. Following the time honoured theses of Virchow, Lubarsch and Aschoff with regard to the evolution of thrombosis we have to consider the alterations brought about by the pneumonia with regard to

1. The haemodynamic conditions,
2. The composition of the blood and
3. The behaviour of the vascular endothelium.

ad (1) The main factors responsible for the adequate venous blood-flow are the muscular tonus, the arterial pulsations and the vis a tergo represented by the beat of the heart. With regard to the muscular tonus its importance has been stressed particularly by Henderson; investigations by Budelmann and co-workers (1939) as well as earlier by Bock have demonstrated a reduction of muscular

tonus not only during convalescence and generally in bedridden individuals but particularly during infectious disorders and especially in pneumonia (method of Beiglböck and Junk). It is obvious that this reduction of muscular tonus will be conspicuous not least in the lower extremities of a bedridden patient, for example in the *planta pedis*, where the venous basin, supplied with blood from the arterial system described by Ask-Upmark (1938), will be particularly liable to suffer, since its circulation is so very much furthered by the use of the feet; it is well known that this plantar basin quite often will represent the source of thrombosis (cfr the tenderness on pressure exerted towards calcaneus).

As to the arterial pulsations it is a general arrangement of the veins of the extremities to accompany an artery; as a rule two veins will run along one artery, connected with one another by anastomotic branches around the artery, so that they are bound to receive the pulsations of this vessel (Ask-Upmark). The structure of the wall of the arteries of the extremities favour the amplitude of the pulsations (contrary to the intracranial arteries, cfr Wolf 1938) and the rhythmic pressure impulses transmitted to the adjoining veins will drive the venous blood in the direction indicated by the *valvulas*. This physiological arrangement seems, as a matter of fact, to be of paramount importance.<sup>1</sup> Any factor liable to reduce the blood pressure or the arterial amplitude will facilitate the occurrence of venous stasis. In pneumonia the impairment of the heart on the one hand, the involvement of the peripheral vasomotor tonus on the other invite a reduction of the blood pressure, which may be noted during the course of the pneumonia (when it however also may increase) but particularly after the crisis (Reimann, 1938). Another factor, which may be of importance in this connection, is the observation of Naumann (1939) that the arterial pressure in the lower extremities, which in normal individuals is at least as high and often higher than in the arms, during the course of infectious disorders may be lowered below the brachial level.

With regard, finally, to the condition of the heart in pneumonia it is obvious that the heart (as well as the vascular centre and the vasomotor periphery) will suffer from the toxemia, from the increased venosity of the blood and from the increased load repre-

<sup>1</sup> In Graves' disease, where TIE is rare, this arterial amplitude is considerably increased.

sented by the increased demand of the tissues for oxygen and perhaps occasionally also by the diminished arterial bed in the lungs: Reimann states that myocardial degeneration should be found in almost one half of the patients studied at necropsy. Although the general impression of the circulatory failure to be noted in pneumonia is that of »forward failure» it is obvious that the impaired condition of the heart may represent a contributory factor. The old experience of the greater frequency of TE in individuals with affected heart (old people, fat individuals etc.) is in line with this assumption. In coronary thrombosis TE is met with much more often than in pneumonia and perhaps more often than in any other internal disorder (Ask-Upmark, unpublished observations); although the importance of the vasomotor collapse in this connection is outstanding the primary importance of the affection of the heart should not be forgotten.

Last but not least should be remembered that the mechanical conditions present in a person lying down on his back, hardly are liable to facilitate the venous circulation of the legs: on the one hand the direction of the femoral vein is by no means horizontal but rather much up-hill towards the inguinal region, and the same may be said of the pelvic veins; on the other hand the pressure of the abdominal organs rests upon the cava system and the veins of the calves are liable to be compressed by the weight of the legs (cfr the observations of Berblinger about the necroses of the muscles of the calves in bedridden individuals). If a urinary retention should be present (more often of course after an abdominal operation than in pneumonia), the venous drainage of the pelvis is liable to suffer, being deprived of the pressure impulses exerted by the constantly variable size of the bladder.

ad (2) With regard to the composition of the blood in pneumonia it is obvious that several features are to be encountered which at least apparently will facilitate the evolution of thrombosis. The increased venosity of the blood (cfr Stuber and Lang 1930 and others), the quite considerably increased fraction of fibrinogen (cfr Frey 1928, Hecht Johansen 1933, Reimann 1938), and the behaviour of the blood platelets (Reimann 1938, Heinild 1942) are such characters. It should be observed that the fraction of fibrinogen will be increased particularly about the time of crisis and for some few weeks afterwards, and that the blood platelets, reduced as in all in-

fections during the febrile period, surge above normal level at the crisis and remain high for at least a fortnight. The coincidence in time between these features on the one hand, the occurrence of TE on the other makes it tempting to consider the matter of at least contributory importance.

On the other hand it should be observed that the characters just mentioned may occur without any TE, and that fibrinogen and thrombocytes only are to be considered as raw material, supplied by nature for the development of TE but by no means as the primary factor in the sequence of events resulting in TE. As Lenggenhager (1941) rightly puts the matter: »In diesem Überangebot von gerinnungsfähigen Substanzen . . . benötigt die Gerinnung ebenso nicht wesentlich kürzere Zeit, wie ein Kilogramm Schiesspulver nicht wesentlich rascher abbrennt als ein Gramm.« In the system of clotting, however, there are two antagonistic principles to be considered: on the one side the thrombokinase (Morawitz-Mellanby = thromboplastin of Howell = thrombokinin of Lenggenhager), which invites clotting by transforming prothrombin into thrombin and which is said to be present in all tissues but particularly in lung and brain, on the other side the heparin, which prevents clotting by neutralizing thrombin<sup>1</sup>, assisted by another substance present in circulating blood (an albumin, termed by Lenggenhager metatrombinogen). By the ingenious investigations of Jorpes and Hjalmar Holmgren it has been established beyond reasonable doubt that heparin is produced by the »Mast-Zellen« of Ehrlich, which are present all over the body, mainly arranged in a perivascular way. Various animals do present the bulk of »Mastzellen« in various organs (the cow in the capsule of the liver, the rats in the skin, etc.). Already the Toronto school, however, did find out the large amounts of heparin which were to be obtained from the lungs (cfr Jorpes), and this observation has been histologically substantiated by the studies of Holmgren: the amount of Mastzellen in the lungs may be somewhat variable in the various species, but they were always present. It should be emphasized that the

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<sup>1</sup> This is the conception of Mellanby, most generally accepted. According to the old aspect of Howell the action of heparin was to prevent the conversion of prothrombin into thrombin; according to the recent hypothesis of Lenggenhager the main effect of heparin should be considered the neutralization of thrombin, although it should also stabilize the prothrombokinin and block the effect of thrombokinin.

lungs assume a privileged position with regard to the blood supply in as much as every drop of blood has to pass the pulmonary capillaries in order to perform the circle. The involvement of the lung or part of it in a severe pathological process as pneumonia is no doubt liable on the one side to liberate quite a lot of thrombokinase in the circulation, on the other side to paralyse the activities of the Mastzellen, not only in the involved part of the lung but reasonably also in the rest of the body (cfr below). Just as we may encounter jaundice or albuminuria or cerebral symptoms during the course of a pneumonia we may of course just as well encounter a damage to the heparin-producing parenchyma. It is possible that this aspect may enable an understanding of the occurrence of TE in pneumonia.

ad (3) As to the vascular endothelium several authors have tried to make alterations of this structure responsible for the development of TE. These attempts have been based mainly on two series of observations: on the one hand the analogy with the conditions in the arterial system, where atheromatous changes are believed to facilitate the evolution of thrombosis, on the other hand certain experiments in animals, carried out especially by Ritter and by Dietrich. Ritter obtained histological changes of the vascular endothelium by intravenous injections of vital dyes, of micro-organisms and of protein substances. Dietrich by the same means allegedly sensitized the endothelium and eventually, under certain conditions, did observe thrombosis and occasionally even embolism. Valid objections have however been raised against this interpretation of an endothelial factor in the pathogenesis of TE: they have been reviewed to some extent by Geissendörfer (1936), by Silberberg (1938) and by Lenggenhager (1941) where references and details are to be had.

Briefly summarized, the main objections are 1. that alterations of the venous endothelium may occur without any subsequent thrombosis (for example when the vein is sutured after thrombectomy or in connection with intravenous injections), 2. that no anatomical alterations of the vascular endothelium hitherto have been demonstrated in early instances of human TE (Aschoff), 3. that numerous conditions in clinical pathology invite to endothelial reactions without inducing any particular occurrence of TE, 4. that such recent instances of thrombosis, where the obliteration of the vascular lumen is only partial, are not circular but do present an adhesion to the venous wall only

in the lower half of the lumen (following the gravity). The opinion seems warranted that, at the present time, there seems to be no reason to attribute an outstanding role to the endothelial factor in the pathogenesis of TE.

On the other hand it should be readily admitted that the question of the endothelial response is not entirely untangled. It should thus be observed that at least when thrombophlebitis is about, an alteration of the wall is present, whether primary or secondary remains to be settled. It should further be remembered that, to the best of my knowledge, no investigations seem to have been carried out of the histological behaviour or that venous plexus which represents the plantar basin. That this venous system is likely to represent the source and the matrix of at least a large part of the clinical instances of TE has already been emphasized. In this connection it seems not out of the way to recall the rather unique physiology of the vascular system of *planta pedis*: Danish authors have demonstrated that the diurnal alterations of the temperature of the skin is of quite another magnitude in this region than in any other area of the body surface and that prognostical conclusions may be drawn from the behaviour of the temperature of *planta pedis* in connection with narcosis and surgical interventions. It seems entirely possible that an interference with the vasomotor regulatory mechanism here concerned (whether caused by an operation or by a severe febrile condition such as pneumonia) may represent a contributory factor in the sequence of events responsible for the development of thrombosis, it may be admitted, however, that even if such be the case the vasomotor factor rather will be of haemodynamic than of endothelial character.

Briefly summarizing the discussion it may be concluded that haemodynamic factors are likely to be of importance for the evolution and localization of thrombosis in pneumonia, that however the primary cause seems to be the affection of the clotting mechanism of the blood, and that hitherto no definite evidence is available about any importance of the vascular endothelium. The hypothesis has been marshalled that a central position in the pathogenesis of TE is represented by the presumed affection of the basophil parenchyma, the entity of heparin-producing »Mastzellen». Further investigations will have to demonstrate whether this aspect is to be haematologically and histologically corroborated. It should, how-

ever, be emphasized, on the one hand that a functional lesion by no means always is to be anatomically substantiated (cfr those instances of diabetes mellitus with morphologically normal insular structure!), on the other hand that this aspect seems to be well compatible with our present knowledge about the clinical behaviour of TE: the occurrence in certain individuals, the possibility of prevention viz. of combating the further development by the use of heparin, and the hitherto enigmatic chronology of its appearance (vide infra). It is perfectly obvious that the aspect here mentioned by no means does exclude the importance of other, contributory mechanisms: the salient feature seems to be the balance between, on the one side thrombin, as determined by the amount of thrombokin<sup>in</sup> liberated from the damaged or diseased tissue and by the ability of the liver to eliminate the thrombin (cfr Lenggenhager), on the other side antithrombin, as determined by the heparin and the metatrombinogen available. If, for example, the amount of thrombokin<sup>in</sup> should be considerable (after a major surgical operation or a severe internal disease such as pneumonia) even a slight reduction of the heparin production might mean insufficient protection against TE. It should however be remembered that thrombokin<sup>in</sup>, according to Mellanby, is prone to neutralize the action of heparin.

The validity of the hypothesis thus outlined may be tested morphologically by determining the number of basophil Ehrlich cells in connection with disorders liable to present TE (this line of research scheduled in the Medical Clinic at Lund), chemically by investigating the neutralization of thrombin by antithrombin, along the lines indicated by Lenggenhager; the demonstration by this author that the impaired inactivation of thrombin is due not to any increased amount of thrombin but to its reduced destruction seems to be entirely compatible with the aspect here marshalled.

The following are some features of the TE disorder which might become understandable by the interpretation already suggested:

1. Certain individuals do obtain TE, others not. The constitutional disposition seems to be substantiated by racial differences (Holm found no TE whatsoever during about 2 years in the hospital of Lambarene in equatorial Africa, where negroes were taken care of surgically and medically), by the old observation of a »typus

angina). In this sense it may even be spoken of an allergic mechanism. This, of course, is only one of several possible explanations<sup>1</sup>, other factors (e. g. of haemodynamic character) may be involved as well.

Other hitherto enigmatic observations in connection with TE (for example the apparent predilection for abdominal operations) might be explained as well but the examples given may be sufficient to elucidate the handiness of the theory here suggested.

### Summary and conclusions.

1. Contributions to the problem of venous thrombosis and pulmonary embolism (TE) have been numerous from surgery, only scanty from internal medicine, owing no doubt to the fact that only few internal disorders, complicated by TE, allow the establishment of a definite time table between the primary disease and the secondary evolution of TE. Such internal disorders are, however, pneumonia, coronary thrombosis and certain instances of pernicious anemia. The present study is concerned with the occurrence of TE in pneumonia.

2. The material was represented by 1454 cases of lobar pneumonia, observed in the Medical Clinic at Lund during the years 1916—1941. TE was observed in 27 instances, i. e. in about every 50th case. 11 cases were males (1.1 %), 16 cases females (3.4 %). Persons above 40 years were afflicted somewhat more often than cases below this age (males 1.5 % versus 0.9 %, females 3.7 % versus 3 %). During the last 4 years (1938—1941) more instances of TE have been taken to the records than during the preceding 22 years, owing no doubt to the introduction of specific therapy which allows cases to survive and develop TE who previously might have succumbed in pneumonia at an early stage. The average time elapsed between the onset of pneumonia and the onset of TE was 13 days, the average time elapsed between the crisis and the onset of TE was 8 days. For reasons developed in this paper this period of time should be considered as somewhat less than the dates just indicated. The evolution of TE is particularly to be feared in such instances of pneumonia where the temperature does not attain nor-

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<sup>1</sup> Whether for example the basophil cells should in any way be engaged in the lysis of pneumonia remains to be seen.



mal level at the crisis resp. viz. lysis, but it may occur even if this level is reached.

3. The observations hence recorded are discussed. Haemodynamic factors favouring the evolution of TE are the reduction of muscular tonus, the impairment of the blood pressure and the involvement of the heart. Haematological factors are the increased vènosity of the blood, the increased amount of fibrinogen and the increased amount of thrombocytes but probably particularly the behaviour of thrombin. The hypothesis is marshalled that a salient feature in the pathogenesis of TE is represented by the impairment brought about by the pneumonia of the heparin-producing »Mastzellen» parenchyma.

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From the Blegdamshospital, Copenhagen. Physician-in-chief:  
Professor, Dr. H. C. A. Lassen.

## Experiments with the Transmission of Infectious Mononucleosis to Man.

By

JENS BANG.

(Submitted for publication November 6, 1942).

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In an earlier paper [Bang (1)] dealing with attempts to transmit infectious mononucleosis to monkeys, the author has touched on the problems involved in the etiology of this disease, problems which have not yet been satisfactorily solved. Extensive investigations on the etiology of mononucleosis — including attempts to cultivate a specific bacterium from patients with the disease, as well as attempts to produce mononucleosis experimentally in animals — have been carried out by Stig Thomsen (2) in Denmark and Per J. Wising (3) in Sweden. Reference is made to the work of these authors, who, like several others including the author of the present paper, were unable to find any support for the assumption of a bacterial etiology. This circumstance has naturally led to the idea that infectious mononucleosis is a *virus disease*, a conception which also finds support in other facts (1) (2) (3).

But even though time seems ripe at last to bury the hypothesis of bacterial origin, we are still in need of the final proof of the virus theory. It is the object of the present investigation to elucidate the problem by means of experiments dealing with the *transmission of infectious mononucleosis to man*. Although the results of these

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<sup>1</sup> The investigations have been supported financially by P. Carl Petersen's Foundation.

experiments so far have been *negative*, they deserve a brief mention, if for no other reason than to show that a direct transmission of mononucleosis is not a simple matter.

Experiments of this kind have already been made by Wising(3) who very recently seems to have succeeded in bringing about a transmission, a report which is of the greatest interest. He injected heparinized blood from patients intravenously into 5 volunteers, of whom one, who had received 250 cm<sup>3</sup>, in 18 days developed symptoms of infectious mononucleosis.

### *The author's experiments.*

Before Wising published this result, experiments were under way at the Blegdamshospital, the present author first attempting to transmit the disease to himself, then to some medical students who were fully advised of the risk.

A total of 19 experiments have been made, involving 15 individuals, 3 of them participating more than once. The volunteers were in the age from 21 to 24 years (with one exception who was 33), thus within the age-class where infectious mononucleosis occurs with the highest frequency. As far as it was known, none of these volunteers had previously had the disease. The material used for the inoculation was obtained from 15 patients, all representing typical cases of the disease, all severely affected, and all in an early febrile stage and with positive Bunnell's test. Table I contains a survey of the supposedly infectious material from the patients and of the inoculation methods tried out.

Since it could not be known beforehand what materials had the best prospect of containing the hypothetical virus, and what inoculation methods had the best chance of obtaining response, the only thing to do was to proceed by way of trial. Dealing with human subjects, however, kept the ingenuity within bounds and called for certain precautionary measures. Thus, in view of the risk of giving the volunteer other and undesirable diseases, infectious material from tonsils and fauces could only be applied after bacterial filtration, even though there was a chance in such a procedure that the hypothetical virus did not pass the filter. It is likewise obvious that the number of different methods (and places) of inoculation was more limited than in experiments on animals and it was necessary

Table I.

*Materials and inoculation methods employed.*

| Volunteer No. | Material obtained from the patient   | Inoculation method  |
|---------------|--|---|
| 1, 2, 3       | a) Bacterial-filtered rhinitic and sinusitic discharge<br>b) Bacterial-filtered suspension of tonsil scrapings | a) Inoculation in nose and throat<br>b) Inoculation in tonsils  |
| 1, 2, 4       | Lymph node emulsion  | 1 cm <sup>3</sup> injected subcutaneously   |
| 5             | do   | 2 cm <sup>3</sup> subcutaneously and<br>2 cm <sup>3</sup> intramuscularly                                   |
| 6             | do   | Oral ingestion  |
| 7, 8          | Bacterial filtered tonsil emulsion   | 4 cm <sup>3</sup> subcutaneously and<br>2 cm <sup>3</sup> in nose and larynx                                |
| 1, 6, 9       | Heparinized blood  | 20 cm <sup>3</sup> intramuscularly  |
| 10            | do   | 20 cm <sup>3</sup> intravenously<br>20 cm <sup>3</sup> intramuscularly<br>10 cm <sup>3</sup> subcutaneously |
| 11            | do   | 50 cm <sup>3</sup> intramuscularly  |
| 12            | do   | 300 cm <sup>3</sup> intravenously   |
| 13            | do   | 325 cm <sup>3</sup> intravenously   |
| 14            | do   | 250 cm <sup>3</sup> intravenously   |
| 15            | do   | 300 cm <sup>3</sup> intravenously   |

to refrain from any action which might lower the resistance. The Wassermann reaction of the patients was, of course, negative.

The different methods tried will be seen from the table, to which a few supplementary comments may be added. The bacterial filtration was carried out by means of a Seitz E. K. filter; incubation tests proved the filtrates to be sterile. The lymph node emulsions were prepared from freshly extirpated, swollen, inguinal lymph nodes which in a sterile mortar were ground up with sand and emulgated in 2 to 3 times the amount of physiologic salt solutions, whereupon sand and coarser particles were centrifuged off before the injection; cultivation on the usual substrates proved these emulsions to be sterile. Heparinized blood was used, like the lymph node emulsions without bacterial filtration. Incubation tests showed no bac-

terial growth. The intravenous inoculations were carried out like ordinary blood transfusion, after determination of type. The tonsil emulsion was prepared from tonsils which were removed by immediate tonsillectomy; the tonsils in question were the seat of a very considerable acute swelling and redness, and were covered with membranes and ulcerations. The emulsion was prepared like the lymphatic node emulsions, but was subjected to bacterial filtration before the inoculation. It may finally be added with respect to the somewhat drastic alimentary experiment that the freshly prepared lymph node emulsion, without further treatment, was swallowed by an undismayed student.

Before the experiments the volunteers were all in good health; all showed hematologically normal conditions, and serologically the test for sheep red cell agglutinins (Bunnell's test) was negative, (case 14 not tested). The volunteers were watched with a view to clinical symptoms, the white blood picture and Bunnell's test, for 4 to 6 weeks after the inoculation. While none of them developed clinical or hematological signs of infectious mononucleosis, the inoculation was in some instances perceptible in the *serological conditions*, 5 of the volunteers who had received injection or transfusion of blood showing the presence of sheep red cell agglutinins, as seen from table II.

There is nothing striking in the fact that the introduction of patient's blood with a high Bunnell titer can be traced for some time in the blood of the experimental subject. It will be seen that the titer in the first 4 cases was below the bottom limit of specificity, and that the Davidsohn differential test was negative. The last case (case 14) was different — here the Bunnell test showed a titer of 1:64, and a positive Davidsohn differential reaction on the day after this volunteer had received a transfusion of 250 cm<sup>3</sup> of blood from a patient. Since this blood on the day in question showed a Bunnell titer of 1:1024, the reaction of the experimental subject finds its natural explanation in the dilution to which the donor's blood had been subjected in the recipient's blood. Thus it is here a question of a process which by its nature is analogous to «passive immunization», since it would be absurd to imagine that the experimental subject should have been infected immediately and produced the antibody in the course of 24 hours. There is something remarkable, however, in the circumstance that the reaction persisted for

Table II.

*The Bunnell test in 5 experimental subjects who showed presence of antibody.<sup>1</sup>*

| Volunteer No. | Patient's blood employed  | Agglutination        |        | The Davisohn differential test |
|---------------|---|----------------------|--------|--------------------------------|
|               |   | Day after experiment | Titer  |                                |
| 10            | 20 cm <sup>3</sup> intravenously<br>20 cm <sup>3</sup> intramuscularly<br>10 cm <sup>3</sup> subcutaneously | 5th                  | 1: 8   | —                              |
|               |   | 12.                  | 1: 32  |                                |
|               |   | 17.                  | 1: 16  |                                |
|               |   | 25.                  | 1: 8   |                                |
|               |   | 30.                  | 0      |                                |
| 11            | 50 cm <sup>3</sup> intravenously  | 15th.                | 1: 16  | —                              |
|               |   | 22.                  | 1: 32  |                                |
|               |   | 32.                  | 1: 8   |                                |
| 12            | 300 cm <sup>3</sup> intravenously   | 7th.                 | 1: 8   |                                |
|               |   | 15.                  | 0      |                                |
|               |   | 30.                  | 0      |                                |
| 13            | 325 cm <sup>3</sup> intravenously   | 3rd.                 | 1: 8   |                                |
|               |   | 10.                  | 0      |                                |
|               |   | 30.                  | 0      |                                |
| 14            | 250 cm <sup>3</sup> intravenously   | 1st.                 | 1: 64  | +                              |
|               |   | 5.                   | 1: 64  | +                              |
|               |   | 12.                  | 1: 128 | +                              |
|               |   | 17.                  | 1: 64  | +                              |
|               |   | 21.                  | 1: 32  |                                |
|               |   | 28.                  | 1: 32  |                                |
|               |   | 32.                  | 1: 32  |                                |
|               |   | 42.                  | 1: 16  |                                |
|               |   | 53.                  | 1: 8   |                                |
|               |   | 63.                  | 0      |                                |

so long. As late as on the 17th. day the titer was 1: 64, and did not reach 0 until the 63rd day. It seems a natural question to ask whether, besides the »passive immunization», there should have occurred, at a later date, a process analogous to »active immunization», i. e., whether the experimental subject received, with the blood from the patient, not only antibody, but also antigen which then gave cause for the production of antibody. The question must

<sup>1</sup> The author is indebted to Dr. Martin Kristensen, Departmental Manager of Statens Seruminstitut, for the making of the agglutination tests.

remained unanswered, since we have no experience to show how long a passive immunization of this kind can be reflected in the blood. It may be added that individual differences seem to assert themselves — otherwise it cannot be explained how two other volunteers (Nos. 12 and 13) showed only a minimal and temporary reaction after the blood transfusion, a third (No. 15) no reaction at all.

### Conclusions.

From the fact that these 15 experimental subjects proved to be refractory to the attempts to produce an experimental infectious mononucleosis it would be premature to conclude that the disease cannot be transmitted, or that it does not depend on a filterable virus. As mentioned above, Wising succeeded in obtaining response in one case where there could be no doubt that the experimental subject actually did get infectious mononucleosis, and where it would be unnatural to question the causal connection between inoculation and disease, suggesting instead the possibility of a «chance coincidence». Nevertheless, one must await with interest whether this experiment can be repeated.

It is apparently not easy, notwithstanding the use of rather drastic measures, to infect human beings. This is not surprising, though, when considering that we have numerous other examples to show that definitely infectious matter may be introduced into an organism without producing disease — compare, for example, the high frequency with which *brucella abortus* Bang occurs in milk with the rarity with which it «takes», or consider foot-and-mouth disease which can occur spontaneously, but which it so far has been impossible to transmit to man.

We know nothing whatever regarding the conditions which are required if the hypothetical mononucleosis virus is to «take». It is believed that the method of inoculation (inclusive the magnitude of the dose) is of less importance than the chance of having to do with an experimental subject whose disposition towards the disease for some unknown reason just happens to be right, or whose general and perhaps specific resistance for some reason or other is reduced.

### Summary.

15 volunteers proved refractory in attempts to transmit infectious mononucleosis. From 15 patients with typical and severe cases of the disease, there were obtained bacterial-filtered materials from the tonsils and the pharynx, unfiltered lymph node emulsions, or heparinized blood. Bacteria could be demonstrated neither in the lymph nodes nor in the blood. The material in question was administered by inoculation into the pharynx, by ingestion, by subcutaneous or intramuscular injections, or by intravenous infusions. Some of the volunteers showed the presence of sheep red cell agglutinins, which finds its explanation in the passive acquisition through the inoculated blood from the patient.

The negative experimental results do not contradict the theory of a virus as the specific agent in infectious mononucleosis, but only shows that it is apparently a question of special luck when producing the infection experimentally — a circumstance which confirms the impression we have already of a slight receptibility. The fact that Wising succeeded in transmitting the disease is an exceedingly strong support of the infection theory, and, taken together with the numerous negative bacterial investigations, is very much in favour of the idea that the disease is due to a virus.

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The author wishes to thank most sincerely the medical students who so willingly placed themselves at his disposal in these experiments.

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From Vestfold County Hospital, (Norway) Med. Dept. Chief: Dr. med.  
Anton Jervell.

## **A Case of Transient Pulmonary Infiltration with Eosinophilia, with fatal issue after treatment by adrenalin spray for asthma.**

By

OLE JACOB BROCH, Tönsberg.

(Submitted for publication November 14, 1942).

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Since Löffler in 1932 first described the transient pulmonary infiltrations with eosinophilia quite a large amount of literature has been published on the subject. The condition has also been very fully described in Scandinavian literature. In so far there would seem to be little justification for adding a new example to the series, but the case which shall here be reported has claims to attention on two points. It represents a fatal case of poisoning from very minute quantities of adrenalin. Fatal results of spraying with adrenalin do not seem to have been previously reported. Moreover, a post mortem examination was made in this case, which is, of course, very rare with such an extremely benign affection as these transient infiltrations of the lungs. And from the literature at present accessible it does not seem that post mortem examinations have hitherto been reported.

Earlier Scandinavian publications give a detailed account of the condition. The reader is therefore referred to the works of Gravesen, Juhlin-Dannfelt, Hansson, Söderling, Tönnesen and others.

Some points respecting the etiology and pathogenesis which are of interest for the case may here be recapitulated. From the literature it appears that the condition does not constitute a sharply de-

finer pathological unit. It must be regarded as a syndrome with varying pathogenesis. Löffler himself distinguished between temporary infiltrations of decidedly tuberculous etiology, with some analogy to erythema nodosum, and transient infiltrations in tuberculin-negative subjects. These latter he regarded as pneumonia-like infiltrations in allergic individuals.

It may be questionable whether such a non-characteristic symptom as eosinophilia can be taken to delimit a pathological unit. Westergren holds that eosinophilia in lung affections tells nothing as to the etiology, but is merely expressive of a special irritation, particularly in the hilus region. He has observed eosinophilia in a number of different pulmonary diseases. On the other hand, there have been described numerous cases of transient infiltration of the lungs without eosinophilia which must be regarded in the same manner as the cases where eosinophilia is present. During the epoch of tuberculin treatment eosinophilia was frequently observed as an indication of allergisation of the organism. Leitner has described a number of such temporary infiltrations, accompanied by eosinophilia, in tuberculous individuals. He calls them tuberculous, hyperergic infiltrations and believes them to be due to an endogenous tuberculisation. Of etiological interest are also the 7 cases reported by Hedvig Adlercreutz, which in the course of a comparatively short time occurred epidemically within a small area. There was close contactual infection between the patients. She assumed that the incubation period must be between 3 and 4 weeks. In two cases eosinophilia was distinctly present.

The allergic element has in recent years come more into the foreground and most investigators are inclined to think that the infiltration of the lungs is due to a special allergic reaction, related to asthma and urticaria, in hypersensitive individuals. The condition is also frequently combined with other allergic manifestations (Söderling). By injection of adrenalin Magnusson got the infiltrations to disappear promptly, which, however, Juhlin-Dannfelt failed to do. Busche got them to disappear on injection of calcium. Some allergens have also been found, for example, pollen (Engel and Meyer). Wild and Loertscher described two cases which they thought to be due to a local reaction to ascaris larvae in the lungs. From the heterogeneous group: transient lung infiltrations with eosinophilia, it is therefore fully permissible to separate out a quite

clearly delimited group with *allergic* transient infiltrations. This fact has also influenced the view of the pathogenesis adopted by many investigators. Thus Engel speaks of a circumscribed pulmonary edema. Hansson of «internal exanthemas». Gravesen states that it is the interstitial lung tissue that is hypersensitive, and not the bronchi as in asthma.

nosis of the malady: An infiltration which on X-ray examination is found to have practically disappeared in the course of 20 days. No detrimental influence on the general condition and an extreme eosinophilia belonging to the most severe that have hitherto been observed. The history of the case with the constant attacks of asthma also points distinctly to an allergic reaction. The histological picture must probably also be taken as indicating a local allergic reaction of the tissues, in addition to which we have signs of inflammatory changes. All this supports the conception of these cases as a local allergic reaction of the lungs.

There can hardly be any doubt that the death must be ascribed to the inhalation of adrenalin. She got ill shortly after the inhalation and the picture she presented might be taken to point to adrenalin poisoning. Several cases of death after adrenalin are reported in the literature. Gormsen in 1939 assembled 28 cases and himself reports a death after 60 mg subcutaneously, in which case an autopsy was made. Autopsy was also made by Hval and Thomassen in a case of death after 50 mg. Both patients died a few minutes after the injection. In both cases the autopsy revealed extreme hyperemia in all organs, in the lungs also edema. The high degree of stasis is quite characteristic of adrenalin poisoning.

It is conceivable that in our case the action of adrenalin may in some degree have marked the histological picture, but there are found changes which cannot be explained solely by the effects of adrenalin. They must therefore be regarded as the histological substratum for the infiltration present. The infiltration had become considerably reduced, sufficiently to enable us to establish röntgenologically its transient nature, but not so much as to render the histological picture indistinct. We also fail to find the severe edema usually seen in cases of death from adrenalin poisoning. The explanation undoubtedly is that in this case the mechanism of death has been somewhat different than usual. This subject has recently been dealt with by Knud O. Möller in a paper on the treatment of adrenalin poisoning. Owing to the pulmonary circulation being less susceptible to the action of adrenalin there comes first a failure of the left ventricle. This is the cause of the edema in the lungs, which in some cases may occur comparatively late. Wichels and Lauber's patient died of edema in the lung two hours after injection of 75 mg adrenalin. Pindborg describes a case of late-

arising pulmonary edema and long-continued renal lesion, with cure after 110 mg.

In some cases death may be due to ventricular fibrillation. This must have been the case with our patient. The fibrillation must also have come on rather rapidly, before one-sided failure of the left ventricle could take place. This explains why the stasis and edema in the lungs were not so strongly marked as usual, even though there had existed a general effect of adrenalin.

What quantities of adrenalin can have occasioned the death in this case? Weighed on a microbalance the spraying apparatus showed a loss of about 0.4 mg for each stroke of the balloon, which means that 0.04 mg of pure adrenalin was atomized each time.<sup>1</sup> She used the inhalator «a couple of times». She can therefore hardly have inhaled more than 0.10 to 0.15 mg of adrenalin. It must be assumed that only a minor part comes down into the alveoli of the lungs and can be fully absorbed. A certain effect from the portion that is deposited in the upper air-passages must probably be reckoned with, but undoubtedly to considerably smaller extent. Therefore the effective dose cannot possibly have exceeded 0.10 mg and was *probably considerably less*. How can it then be explained why Pindborg's patient survives a dose more than 1000 times as large, while this patient dies from the effects of a substance which is normally present in the organism, administered in such small quantity that the concentration thereof in the blood hardly reaches higher values than may be found under certain physiological conditions?

According to Kalaja the content of adrenalin in the blood of normal individuals varies between 7 and 11  $\gamma$  per cent. Therefore if we take the patient's original concentration of adrenalin to be 9  $\gamma$  per cent and the added quantity which was absorbed to be at most 100  $\gamma$  (the actual figure was probably a good deal lower), then the adrenalin concentration will rise to a maximum of 11.2  $\gamma$  per cent when the adrenalin is distributed over the whole of the blood, which must be the case if a general effect of adrenalin is to be produced. Accordingly, only a relatively insignificant increase in adrenalin content can have occurred, an increase which falls entirely within the limits of normal variation. Moreover, Kalaja states that he

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<sup>1</sup> Analysis of the preparation at the Apothecaries' Laboratory showed that it contained 9 % adrenalin.

usually found considerably increased values in cases of asthma. *We may therefore be permitted to conclude that the death cannot have been due to an absorptive poisoning with adrenalin.*

In view of these considerations we have imagined the possibility that the patient might have used the inhalator in such manner that some of the adrenalin may have run into the mouth and been swallowed. She could then have taken in quite considerable quantities per os. A peroral action is not out of the question, even though it will be slight in proportion to the parenteral. Troisier and Weiss-Rondinesco have reported case of serious poisoning after 4 mg per os. This possibility must, however, be rejected. Two eye-witnesses stated, quite independently of each other, that the patient was sitting up in the bed when she used the inhalator, that she inhaled through the nose and that she held the apparatus straight up and down. It is therefore quite out of the question that anything can have run out of it.

From the history of the case it appeared, however, that the patient had on an earlier occasion been given an injection of adrenalin. As already mentioned, she had undergone tonsilectomy in the previous year. The doctor who then treated her states that the operation was carried out with the usual anesthetic technique: Painting with adrenalin-pantocain and filtration with 1 per cent of a 20—30 cm<sup>3</sup> solution of novocain-adrenalin (one drop of a 1<sup>0</sup>/<sub>100</sub> solution to 30 cm<sup>3</sup>). This corresponds to 0.03—0.05 mg of adrenalin. It is estimated that about 0.05 mg was used for the painting, but the absorption from the mucous membrane of the mouth will certainly have been entirely negligible. The operation was not attended by any special complications. Thus it is seen that she was given on that occasion without reaction an injection of about the same quantity of adrenalin which on inhalation a year later called forth a violent reaction resulting in death after a few minutes.

That the adrenalin in itself must have been the cause of death is beyond all doubt. But if the death cannot be ascribed to an absorptive action, what did she then die of? There can hardly remain any other possibility than that the local action must in some way or other have released a fatal mechanism. The most probable explanation is that *via* the sympatheticus there arose a reflex action on the heart with ventricular fibrillation as its result. In this way may be explained the fact that she had earlier received more or less

the same quantity of adrenalin injected subcutaneously without any trace of reaction and that the autopsy did not reveal the usual signs of absorptive adrenalin poisoning.

In his list of deaths reported to be due to adrenalin Gormsen rejects no less than 23<sup>1</sup> as being doubtful. In most of these cases the patient had been exposed to other injurious influences (chloroform narcosis, cocain injection or very bad general state of health) and sometimes the information supplied is very incomplete. In these cases the dose has also been small, usually less than 1 mg. After having studied the most of the sources I agree that these cases cannot unreservedly be accepted as pure and convincing examples of death due to adrenalin.

In some cases where subcutaneous injection of adrenalin solutions is being made the injection may by a mischance have come to take place intravenously and in such case severe poisoning will as a rule occur after ordinary doses of adrenalin. When administered intravenously, adrenalin is stated to act about 40 times more strongly than on subcutaneous injection.

These case here described does not, of course, admonish us to any hesitation in the use of adrenalin in ordinary doses and especially not against the spray treatment, which is so convenient and has given relief in so many cases, but the patient ought to get careful instruction when using the apparatus for the first time. The case, however, shows that human reactions are so manifold that no amount of experience is entirely adequate in every case and that a mode of treatment or a remedy which in general entails no risk may yet in a particular individual call forth reactions of disastrous effect in the organism.

### Summary.

A brief survey is given of the etiology and pathogenesis of the transient pulmonary infiltrations with eosinophilia. Among these forms of disease should be distinguished a quite sharply delimited group, which must be regarded as an allergic reaction in the lungs.

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<sup>1</sup> One case must have been included owing to a misunderstanding. This was a patient with horse-asthma who got a violent anaphylactic shock after intravenous injection of extremely small quantities of horse serum. She died half an hour later, in spite of intravenous administration of adrenalin (Broughton; Journ. Am. Med. Ass. 1919: 73: 1913).

A case is described: A woman aged 28 had for about a year been troubled by asthma. While in the hospital she got slight asthmatic attacks and X-ray examination revealed an infiltration about the size of an egg in the right upper lobe of the lung. There was found 70 per cent eosinophilia. She died about five minutes after using for the first time a spray with 10 per cent adrenalin. She had then inhaled only a couple of times through the nose.

On post mortem examination no very conspicuous degree of edema or hyperemia was found in the lungs, such as is usual in cases of adrenalin poisoning. Histological examination showed a thickening of the interstitium in the right upper lobe, with abundant infiltration by plasma cells and lymphocytes. At some places the lung structure was obliterated and the alveoli were distended by different kinds of cells with conspicuous eosinophilia. A few of the bronchi were filled with epithelium and highly eosinophilic leucocytes. Besides there was found at certain places hyperemia and edema. Histological diagnosis: Lung tissue with signs of subacute inflammation and considerable eosinophilia. Post mortem X-ray photography of the lungs showed barely perceptible remains of the infiltration twenty days after it had first been detected. The quantity of adrenalin which brought about death in this case was estimated to be at most 0.10 mg, and probably the portion actually absorbed was considerably less. In the preceding year the patient had undergone tonsilectomy. During local anesthesia there had then been injected between 0.03 and 0.05 mg adrenalin and about the same quantity was used for painting the mucous membrane.

The cause of death was presumed to be a rapidly arising ventricular fibrillation. The possibility of absorptive adrenalin poisoning is, practically speaking, inconceivable in view of the small doses, which could occasion only an insignificant increase of the adrenalin concentration in the blood. The death must then have probably been due to a local effect of adrenalin on the lungs and reflex action on the heart, resulting in ventricular fibrillation.

No such case of death due purely to adrenalin has previously been reported, so far as can be seen from the literature at present accessible.



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(From Kaptein W. Wilhelmsen og Frues Bakteriologiske Institutt, Rikshospitalet, Oslo. Chief: Th. Thjøtta.)

## The Occurrence of Human Intestinal Protozoa in Norway.

With special reference to *Entamoeba histolytica* and *Lambliia intestinalis* and their clinical significance.

By

Dr. med. JOHS. BØE.

(Submitted for publication November 30, 1942).

Investigations on the problem of the occurrence of human intestinal protozoa and the clinical significance of these parasites have especially been called forth by the work of Clifford Dobell and co-workers (1) during and after the war 1914—18. Their investigations made it common knowledge that even the «tropical» parasite *Entamoeba histolytica* regularly occurs in temperate zones. This fact has been confirmed by many investigators from different countries in Europe and from U. S. A. And from Scandinavia we have the work from Sweden and Finland by Ruth Svensson (2) which demonstrates that the same holds true even in northern countries.

In recent times this problem of the human intestinal protozoa has gained even more actuality as many investigators have claimed the great pathogenic significance of these parasites in the temperate zones, and especially since «amebiasis» has become a clinical term. The view held by Craig (3) and many others is, that in temperate zones, infection with the pathogenic amoeba does not cause dysentery but in the majority of cases it is accompanied by much milder symptoms usually not recognized as the result of this infection.

The problem of the pathogenicity of *Lamblia intestinalis* which is not by far solved, and which will be discussed below, has also stimulated investigations in this field.

Human intestinal protozoa have occasionally been found in Norway. The majority of cases are amebic dysentery contracted in the tropics (4, 5, 6, 7). One case of infection with *Lamblia intestinalis* is described (8) and two cases of infection with *Balantidium coli* have been reported (9, 10). But systematic investigations of the occurrence are hitherto not undertaken in our country. Nor are systematic investigations as to their clinical significance reported from the other Scandinavian countries, as the above mentioned work of Svensson does not discuss this side of the problem.

The aim of the present work was first to study the human intestinal protozoa occurring among the healthy population in Norway, and secondly to investigate the pathogenic significance of *Entamoeba histolytica* and *Lamblia intestinalis* in our country.

Patients in medical and surgical wards of three hospitals in Oslo, in total 1111 persons, 510 women and 601 men, were studied. 127 were children under fifteen years.

The specimens were examined according to the usual technic. Only freshly passed stools were examined. All specimens were examined in fresh, unstained preparations and in iodine preparations. In addition, a Haidenhain preparation was made in every case. The usual culture methods for *Entamoeba histolytica* were used during a great part of the work. It was shown that at least 75 % of the infections demonstrated were found by a thorough examination of the first stained preparation. Two specimens were examined from each person.

740 of these patients had no signs of diseases of the gastro-intestinal tract or any other disease which could have any connection with infection with intestinal protozoa. The infections found among these patients (Group I) are — with due reserve — taken as an indication of the occurrence of human intestinal protozoa among the healthy population in Norway. And this group constitutes the normal control material in discussing the question of the pathogenic role of these protozoa.

It was found that infections with human intestinal protozoa were quite widespread in Norway.

Table 1.

*The probable occurrence of human intestinal protozoa among the healthy population of Norway.*

|                                   | Infections demonstrated<br>per cent |       | Probable percentage<br>of infections among<br>the healthy po-<br>pulation |
|-----------------------------------|-------------------------------------|-------|---|
|                                   | Men                                 | Women |   |
| <i>Entamoeba histolytica</i> .... | 2.60                                | 2.25  | 3   |
| <i>Entamoeba coli</i> .....       | 15.32                               | 16.06 | 20  |
| <i>Endolimax nana</i> .....       | 17.66                               | 18.03 | 20  |
| <i>Iodamoeba bütschlii</i> ....   | 8.31                                | 7.61  | 10  |
| <i>Dientamoeba fragilis</i> ....  | 7.01                                | 8.45  | 10 <sup>1</sup>   |
| <i>Lamblia intestinalis</i> ..... | 5.71                                | 4.51  | 7   |
| <i>Chilomastix mesnili</i> .....  | 2.43                                | 2.54  | 4   |
| <i>Trichomonas hominis</i> ....   | 0.78                                | 1.41  | 2 <sup>1</sup>  |
| <i>Enteromonas hominis</i> ....   | 1.04                                | 0.56  | 2   |
| All species .....                 | 45.19                               | 44.51 | 50  |

The table demonstrates that the findings are in accordance with those reported by other investigators from various countries in Europe (1, 2, 11, 12, 13, 14) and from U. S. A. (15, 16.)

Of the actual infections, the infections found must necessarily represent a minimum, the worth of which depend on the technic used. In the last column we have given the figures of the probable occurrence of the human intestinal protozoa among the healthy populations of Norway. And with due reservation to the technic and to the small number of persons examined, we suppose the figures are representative.

In attempting to clarify the clinical significance of infections with these protozoa we examined 371 persons suffering from various gastro-intestinal diseases (Group II). The patients in this group showed a slightly higher infestation with intestinal protozoa than those of group I. But the difference was insignificant as reckoned statistically (17).

52 patients suffering from colitis and 111 patients with indefinite dyspeptic symptoms were examined more thoroughly, as it was to be expected that if «amebiasis» existed, it was to be found in these groups of diseases.

<sup>1</sup> Special investigations might probably give higher percentages.

In these two groups more infections were found than among the healthy persons and among the whole group of patients suffering from gastro-intestinal diseases. But statistically the difference here also was insignificant.

Nor did the clinical investigation of the material give any clear-cut results. Amebic dysentery was not found, and colitic symptoms of any severity could not be related to infection with *Entamoeba histolytica* in a single case. On the other hand, in some cases of indefinite intestinal diseases one could not exclude the possibility that the infection might have played a role in the development of disease. It seems that in northern countries at least, amebiasis is a clinical term not substantiated by facts.

That the amoebae found were fully virulent even when isolated from healthy carriers was shown in experiments on young kittens. From a healthy carrier freshly passed stools containing cysts of *Entamoeba histolytica* were fed to kittens. The typical disease was contracted, and in preparations from the intestine, amoebae were found in the ulcers and in the deep layers of the submucosa.

It was found that the infection could give production of antibodies even when no clinical symptoms were present. 153 sera were examined according to the complement fixation test of Craig (3). Of the four healthy carriers examined one gave a positive reaction. One positive reaction was also found in a patient suffering from an indefinite affection of the liver, most probably a hepatitis or a liver abscess. In spite of many examinations no amoebae could be found in the stools from this patient.

The preparation of an antigen for this reaction has been difficult and uncertain. The author prepared his antigen in the following simple manner: 24 hour old rich cultures of *Entamoeba histolytica* on the usual liver infusion medium were washed and centrifuged five times. The sediment was then a compact mass of amoebae which were exciccated in vacuum and ground to a powder. When used it was suspended in saline, titrated for anticomplementary qualities and used in the reaction in the usual manner. This antigen gave even as good results as the antigen prepared according to the direction given by Craig. As its preparation is very simple, the question of antigen should not prevent the clinical use of the reaction.

It must be concluded from these investigations that the majority of persons infected with *Entamoeba histolytica* have no signs of disease at all. The infection with *Entamoeba histolytica* apparently is of little or no clinical importance in Norway. In a few cases, however, it cannot be excluded that the infection may aggravate or prolong some other gastro-intestinal disease. It may consequently be reasonable to treat the infection when found in a patient suffering from intestinal disease for which no other cause can be found. The healthy carriers need no treatment, and it is not necessary to report the infections to the health authorities.

Next to *Entamoeba histolytica*, *Lambliia intestinalis* has been that of the intestinal protozoa in which clinicians have taken most interest. But in spite of the many clinical and parasitological investigations, the problem of the pathogenicity of *Lambliia* is not by far solved.

The habitat of *Lambliia* is the duodenum and the upper ileum where it may multiply enormously and where it is attached to the mucosa by a sucking disk. The parasite may be so numerous that it may cover the mucosa as a membrane (18). It is also in a few cases reported that *Lambliia* has propagated to the gall bladder (19, 20). Therefore *Lambliia* infections are thought to play a role in diseases of this part of the intestine and the gall bladder.

The clinical manifestations attributed to infections with *Lambliia intestinalis* are numerous. They are often described as a special clinical picture, *Lambliiasis* (21) or *Giardiasis* (22) and the symptoms are most of ten grouped as follows:

1. Acute diarrheas, and symptoms commonly found in chronic entero-colites.

2. Symptoms as seen in chronic gall bladder diseases.

3. Symptoms of more indefinite type, most often nervous symptoms, astenia, fatigue, but occasionally anemia.

The third group of symptoms is thought to be directly produced by a toxic action or may be secondary to the gastro-intestinal disease.

In this investigation *Lambliia* was found in stools from 62 persons aged from two to seventy-six years, 26 women and 36 men. The infection was 38 times found in persons who had no signs of gastro-intestinal disease (group I). In this group the percentage of *Lambliia* positive thus was 5.13. In group II, i. e. among those

suffering from some disease of the gastro-intestinal tract, *Lambli*a was found 24 times, that is in a slightly higher percentage than that of group I, but the difference was rather insignificant.

43 patients with gall bladder disease and 104 with gastric or duodenal ulcer were studied in greater detail. The patients suffering from gall bladder diseases were found to be more often infected than the healthy persons or patients with other gastro-intestinal diseases. But the difference was not conclusive and could not support the view that there is any connexion between *Lambli*a intestinalis and gall bladder disease.

The clinical examination of the patients infected with *Lambli*a gave no clearcut results. In group II including 371 persons with some gastro-intestinal disease, the 24 patients infected with *Lambli*a did not differ in any respect. It was impossible to demonstrate any group of symptoms or even a single symptom which did not regularly occur among the patients not infected with this parasite.

In spite of this, in some cases we had the impression that it was possible or even probable that *Lambli*a had interfered with the health of the patient, but we could not state with absolute certainty that this was so.

In continued investigations including in total 93 infections with *Lambli*a intestinalis (23, 24) we have studied this problem further, partly by treating the infected with atebirin or acranil.

The result has been the same. It has been impossible to demonstrate any clinical picture, *Lambli*iasis, or any symptom related to this infection. But as we have found definite improvement after specific treatment in some cases for which no other causes could be found, we think it probable that in these cases *Lambli*a has played a role in the development of disease. And we find it consequently reasonable to treat the infection when found in such cases.

### Summary.

1. Infections with human intestinal protozoa is quite widespread in Norway. At least 50 % of the population are infected with one or more of these parasites.

The percentages found among healthy persons were as follows: *Entamoeba histolytica* 2.43 %. *Entamoeba coli* 15.68 %. *Endolimax nana* 17.91 %. *Iodamoeba bütschlii* 7.97 %. *Dientamoeba*

*fragilis* 7.70 %. *Lamblia intestinalis* 5.14 %. *Chilomastix mesnili* 2.43 %. *Trichomonas hominis* 1.08 %, and *Enteromonas hominis* 0.81 %.

2. Patients suffering from various gastro-intestinal diseases showed a slightly higher infestation with *Entamoeba histolytica* than healthy persons. But the difference was insignificant as reckoned statistically. The clinical investigation gave no clearcut results. Amebic dysentery was not found, and symptoms of colitis could not be set in relation to infection with *Entamoeba histolytica* in a single case. In some cases of indefinite intestinal disease one could not exclude the possibility that the infection might have played a role in the development of the disease.

Experiments on young kittens showed that the amoebae found were fully virulent.

It was found that the infection might give production of antibodies even when no clinical symptoms were present.

The author presents a simple method for preparing antigen for the complement fixation test.

3. Patients who suffered from gastro-intestinal diseases were more heavily infected with *Lamblia intestinalis* than healthy persons of the same age. The patients suffering from gall bladder diseases were found to be more often infected than healthy persons or patients with other gastro-intestinal diseases. But the difference was not conclusive and could not support the view that there is any connexion between *Lamblia intestinalis* and gall bladder disease.

It was impossible to demonstrate any symptom characteristic of this infection, and even less any clinical picture, Lambliasis.

In some cases, however, it was probable that *Lamblia* had interfered with the health of the patient though this could not be stated with absolute certainty.

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(De l'hôpital de Bispebjerg, Copenhague (Danemark).  
Médecin-chef du Service Médical C.: Professeur Knud Secher, Docteur en  
médecine.)

## Des affections articulaires avec la maladie de Basedow.

Par

EGILL SNORRASON.

(Ce travail est parvenu à la rédaction le 14 Décembre 1942).

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Depuis 1872, où Perry a laissé entrevoir une certaine connexité entre la maladie de Basedow et la «polyarthritides acuta», il a été décrit dans la littérature une centaine de cas, caractérisés par la genèse d'une polyarthrite en même temps que la maladie de Basedow. Comme deux caractéristiques ultérieures de ces cas articulaires spéciaux il faut mentionner qu'ils disparaissent presque «d'une vitesse dramatique» dès que le malade subit une thyroïdectomie, de même que s'ils ne sont pas traités à temps, ils évoluent à des polyarthrites atrophiques avec des contractures caractéristiques. Dans quelques-uns des cas il a, en outre, été décrit une periarthrosis humeroscapularis duplex Duplais — peut-être spécifique — qui se montre assez intraitable par physiothérapie; celle-ci aussi s'améliorait rapidement après thyroïdectomie.

Etant donné que ces affections articulaires n'ont été décrits que rarement — et isolément — dans la littérature, et que j'ai trouvé, pendant les six premiers mois de 1942, un cas prononcé et deux cas débutants à l'hôpital de Bispebjerg, je me permets de les référer — spécialement en vue du diagnostic différentiel du rhumatisme

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chronique déformant (polyarthritis chronica primaria progressiva) et du rhumatisme ostéo-articulaire (polyarthrosis).

Il s'agit de 3 malades, 2 femmes et 1 homme.

1) ♀ (H. H. née 12/10 1890) qui a souffert, depuis 1928, de la maladie de Basedow; glande thyroïde traitée par radiothérapie en 1928—29 à l'hôpital de Øresund, ensuite elle s'est sentie en bonne santé jusqu'au printemps 1941, où des symptômes de la maladie de Basedow prononcés se sont montrés de nouveau (perte de poids, nervosité, palpitations, tremblement des mains, intolérance de chaleur). Depuis novembre 1941 elle a été hospitalisée 3 fois au service médical C. de l'hôpital de Bispebjerg: 11/11—41—20/4—42; 1/6—22/6—42 et 14/7—28/7—42 sous les diagnostics: Morbus Basedowii, arhythmia perpetua, arthropathia manuum. *Objectivement*: exophtalmie observée; glande thyroïde diffusément agrandie; stéthoscopie du coeur: action irrégulière du type arhythmia perpetua sans déficit du pouls. Extrémités: naturelles. Sédimentation globulaire (13/11—41): 1 mm. Pas de polyarthrite aiguë dans l'anamnèse; au printemps 1942 commencement de la ménopause. Le traitement médicamenteux (alitement, diiodotyrosin, digitalan et luminal) donne une amélioration passagère pendant quelques mois (métabolisme basal: 125 %), ensuite l'état s'aggrave (accélération du pouls, perte de poids, métabolisme basal: environ 174 %). On réussit toutefois à améliorer l'état général de nouveau pendant les trois semaines suivantes (les doses de diiodotyrosin sont supprimées); à cette époque, où la température est normale depuis longtemps, la malade commence à se plaindre de douleurs et de gonflement dans la 2<sup>e</sup> articulation phalangienne<sup>1</sup> de l'index et du médius de la main droite et de douleurs à la partie supérieure des deux bras et aux épaules; *objectivement*: on ne trouve ni de rougeur, ni de chaleur aux articulations mentionnées; mais tuméfaction endolorie de la capsule et la mobilité est légèrement diminuée; pas de nodules de Héberden palpables. Dans la période suivante où elle est traitée de stilboestrol et par radiothérapie de la glande thyroïde elle souffre des douleurs ultérieures, diminution de la mobilité et tuméfaction endolorie de la capsule de la 2<sup>e</sup> articulation phalangienne de l'annulaire droit et de l'index, du médius et de l'annulaire de la main gauche ainsi que de la 3<sup>e</sup> articulation phalangienne de l'index, du médius et de l'annulaire des deux mains.

1/6—42, à la nouvelle hospitalisation, on a trouvé *objectivement*: articulation de l'épaule: aucune atrophie musculaire visible. La mobilité est diminuée; côté droit: rotation en dehors: 60°, en dedans: naturelle; côté gauche: en dehors: 0°, en dedans: 60°; abduction: 0—80° mouvements en avant et en arrière des deux articulations des épaules: naturels; aucune crépitation, aucune couche sur le côté de devant des articulations, myoses dans les deux

<sup>1</sup> Les articulations des doigts sont désignées comme suit:

L'articulation entre le métacarpien et la phalange: 1<sup>ère</sup> articulation phalangienne  
 „ „ „ la phalange „ la phalangine: 2<sup>e</sup> „ „  
 „ „ „ la phalangine „ la phalangette: 3<sup>e</sup> „ „

muscles trapèzes, supra- et infraspinaux et les deux bords du deltoïde en avant. Articulations du coude et du poignet: naturelles. Doigts: la peau au niveau des articulations est pâle, luisante, ni suante, ni moite, ni spécialement chaude. Tuméfaction endolorie de la capsule des 2<sup>e</sup> et 3<sup>e</sup> articulations phalangiennes de l'index, du médius et de l'annulaire des deux mains; lesdites articulations sont «ankylosées» dans une flexion volaire d'environ 20°; les pouces n'ayant pas de tuméfaction de la capsule — manquent environ de 5 cm à atteindre la base de l'annulaire en pleine opposition. Il y a une contracture de Dupuytren débutante aux deux annulaires. Pas de nodules de Heberden palpables. (Fig. 1). Extrémités inférieures: naturelles. Sédimentation globulaire 3/6: 2 mm. Température normale pendant le séjour. 14/7—42; elle se plaint toujours de douleurs et de faiblesse des deux épaules et bras, de tiraillements dans les avant-bras et de rigidité aux doigts. *Objectivement*: articulations des épaules, des coudes et des doigts comme 1/6 — à l'exception du pouce *droit* qui ne manque que de 3 cm, et du pouce *gauche* qui ne manque que de 2 cm à atteindre la pleine opposition. Aux deux poignets la mobilité a cependant diminué (*droit*: 0—20°, *gauche*: 0—30°), autant dorsalement que volairement à cause de douleurs par mouvements maximaux; aucun endolorissement au toucher de l'articulation, aucune tuméfaction de la capsule. A l'examen radiographique de la région des poignets et des mains des deux côtés on a constaté un amincissement des scissures des articulations phalangiennes tant pour les doigts de la main *droite* que pour ceux de la main *gauche*. Il en est de même pour la 1<sup>ère</sup> articulation phalangiennes des annulaires et des annulaires. A la tête et à la base des phalanges on observe à plusieurs endroits de petits éclaircissements aux bords des os ressemblant à des déficiences. Au niveau des articulations phalangiennes il y a une tuméfaction des parties molles modérée en forme de fuseau. Pas de chondrocalcinose à proprement parler, mais, toutefois, un éclaircissement légèrement vitreux à la tête des os métacarpiens et à la base des articulations phalangiennes. L'annulaire *gauche* est fléchi à un angle droit à la 2<sup>e</sup> articulation phalangienne. On ne voit nulle part des destructions de la surface des articulations à proprement parler.

Dans les régions des poignets il y a peut-être un amincissement léger des surfaces articulaires, tant entre les os particuliers carpiens qu'entre ceux-ci et les os métacarpiens. (signé: Niels Hansen). (Fig. 2).

En mars-septembre 1942 elle subit un traitement de radiothérapie appliqué à la glande thyroïde en périodes (1050, 900 et 450 r) et de diiodotyrosin, digitalan et stilboestrol.

*Épiscrise*: Il s'agit d'une femme de 52 ans souffrant depuis 1928 de la maladie de Basedow; pendant une aggravation de l'état en 1942 une périarthrosis humeroscapularis duplex évolue avec «ankylose» aux deux poignets et aux 2<sup>e</sup> et 3<sup>e</sup> articulations phalangiennes des index, médius et annulaires; aucune augmentation de

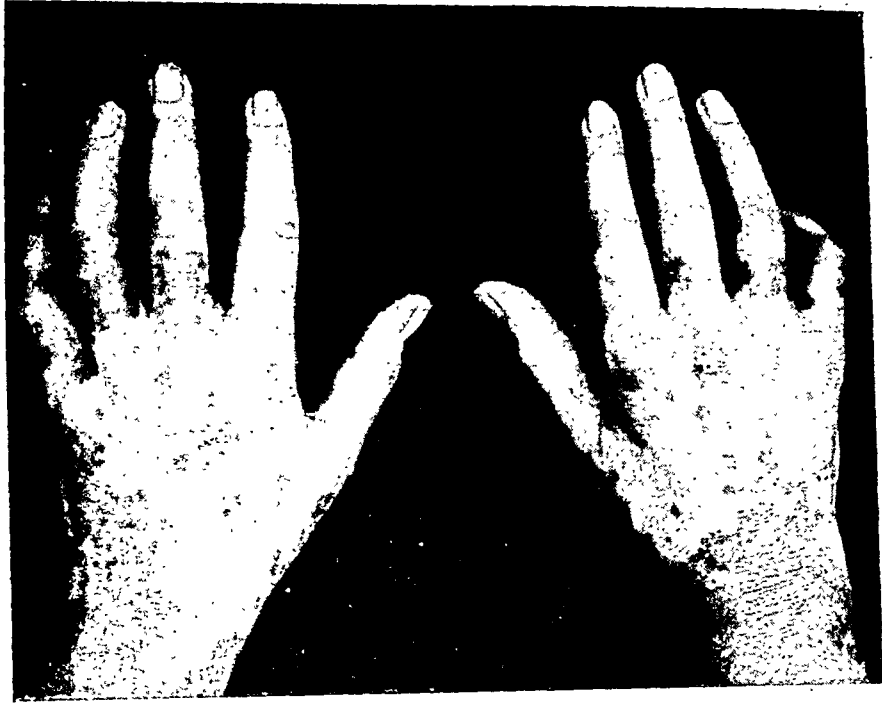


Fig. 1.

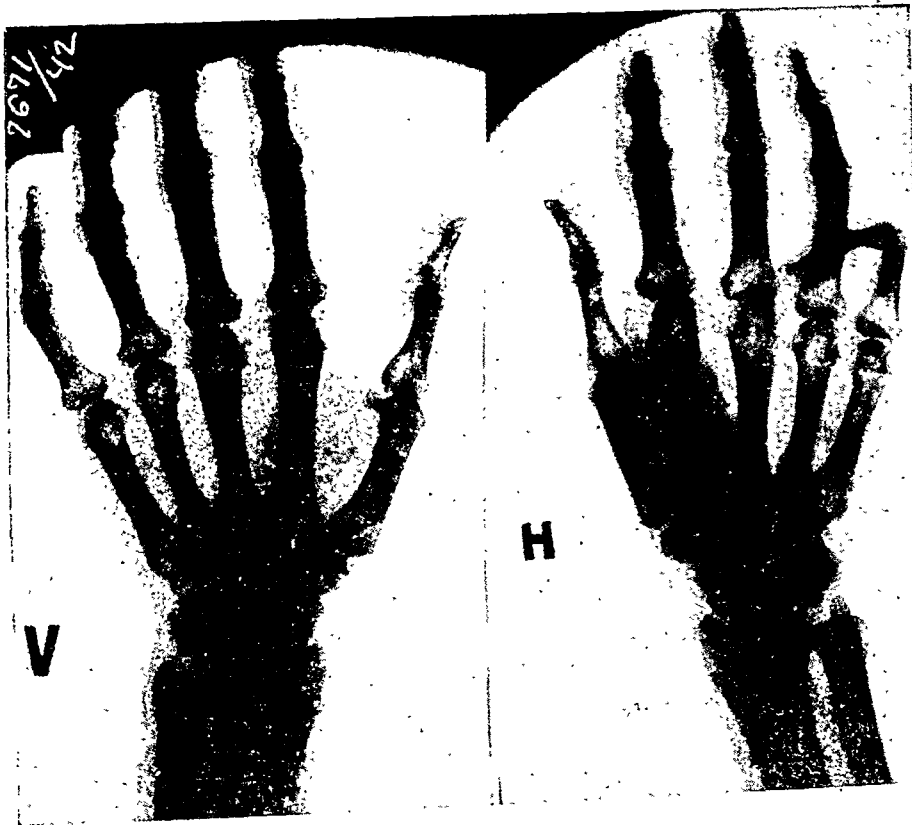


Fig. 2.



Fig. 3.

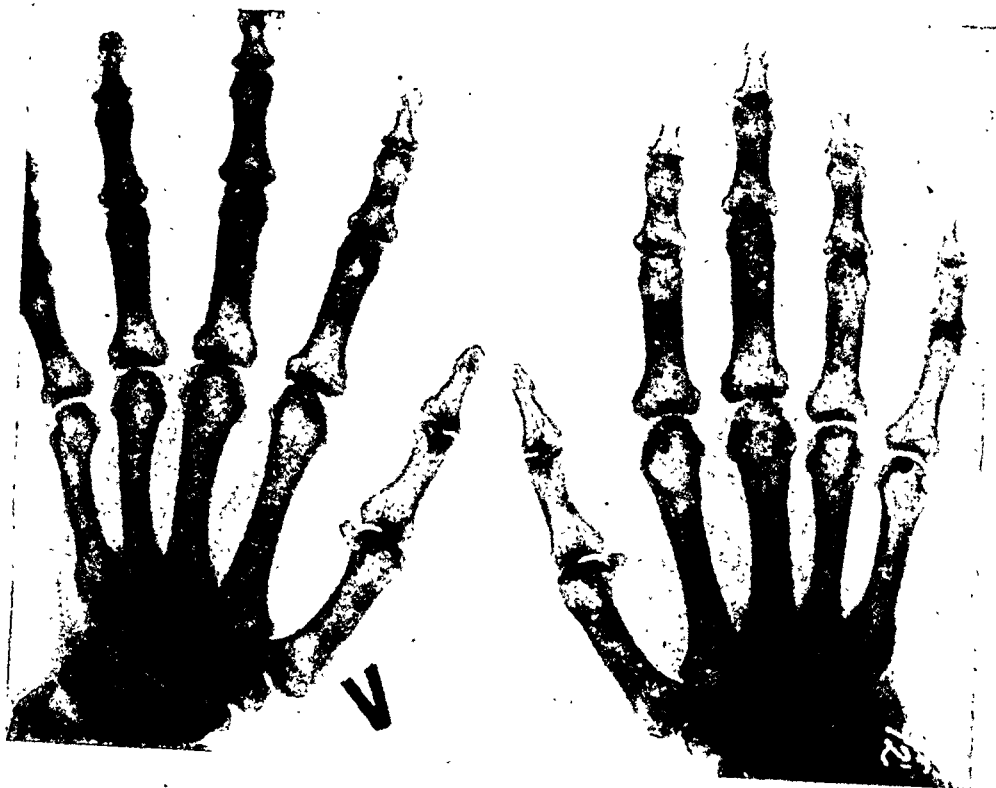


Fig. 4.

température, la sédimentation globulaire est normale et les affections articulaires ne ressemblent ni au rhumatisme chronique déformant, ni au rhumatisme ostéo-articulaire climatérique.

Outre ce cas prononcé, il y avait, parmi les 20 malades souffrant de la maladie de Basedow traités au service au printemps 1942, les deux malades suivants qui semblent présenter les mêmes symptômes articulaires — bien que moins développés que le premier cas mentionné.

2) ♀ (R. H. née 26/7—86) qui a observé elle-même, depuis 1932, un goitre augmentant graduellement; en 1940 apparaissent des symptômes de la maladie de Basedow (perte de poids, nervosité) et depuis le 4/3—42 jusqu'à septembre 1942 elle a été hospitalisée au service médical C. de l'hôpital de Bispebjerg pour: Morbus Basedowii, adenoma thyreotoxicum, arhythmia perpetua. *Objectivement*: exophtalmie, glande thyroïde aggrandie diffusément à un degré modéré, de consistance molle, élastique; stéthoscopie du cœur: action irrégulière du type arhythmia-perpetua avec déficit du pouls d'environ 40. Extrémités: naturelles. Au traitement médicamenteux (alitement, guttae jodi, strofantin, digitalan et luminal) l'état s'améliore bien; comme les métabolismes basaux se trouvent toutefois toujours au niveau d'environ 179—154 % et que le service chirurgical ne désire pas opérer la malade, on l'envoie à la radiothérapie visant la glande thyroïde. — Pendant tout le séjour au service médical C., la température fut sub-fébrile — environ 37° mane et 37.6—8° vespere — elle a été assez enrhumée; traitée par le laryngologiste du service pour ozoena par irrigation et instillation. Sédimentation globulaire légèrement augmentée pendant quelque temps en juin; 7/3: 5 mm, 12/6: 9, 23/6: 17, 6/7: 19, 13/7: 14 et 27/7: 10 mm.

Fin avril 1942 elle commence à se plaindre de douleurs du côté droit du cou rayonnant de l'épaule droite, au bras et à la main droits. Les douleurs sont prolongées, empirées par mouvements; pas de paresthésies, le bras est sans force. Peu de temps après elle commence à sentir les mêmes douleurs à l'épaule et au bras gauches. Dès le commencement de juillet 1942 il y a encore impuissance, raideur, diminution de la mobilité et douleurs à l'index, au médius et à l'annulaire de la main droite et à l'index de la main gauche. La rigidité est localisée aux 2e et 3e articulations phalangiennes des doigts en question; malgré des mouvements actifs et passifs énergiques pendant toute la journée, la rigidité reste. *Objectivement*: l'articulation de l'épaule: aucune atrophie musculaire, mais une couche sur le devant des deux articulations de l'épaule. Mouvements: rotation: 0—30° dans chaque direction, abduction: 0—70° et mouvement en avant: 0—90°, mouvement en arrière: naturel — tous les mesurages valables pour les deux côtés, aucune crépitation. Myoses aux deux muscles trapèzes, supra- et infraspinatus, aux deux bords de l'avant et de l'arrière du deltoïde, ainsi qu'au groupe radial droit. Articulation du coude: douleurs dans l'extension jusqu'au maximum, aucun gonflement, ni de rougeur des articulations. Poignets: naturels.

Doigts: peau chaude, moite, d'ailleurs naturelle. Tuméfaction endolorie de la capsule ni chaleur, ni rougeur des 2e et 3e articulations phalangiennes de l'index, du médus et de l'annulaire de la main *droite* et de l'index *gauche*. La mobilité est diminuée, de sorte que l'index *droit* manque de 2 cm, le médus *droit* manque de 1 cm, et l'annulaire *droit* manque de  $\frac{1}{2}$  cm à atteindre la paume, tandis que l'index *gauche* y manque de  $\frac{1}{2}$  cm. Tuméfaction modérée de la capsule, aucune ankylose des articulations observée, même s'il existe des difficultés à les étendre. Nodules de Héberden palpables aux deux index — toutefois, la malade ne les a jamais remarqués elle-même. Aux deux auriculaires contracture de Dupuytren débutante — de même que des vitilignies ont commencé à apparaître, correspondant aux 2e et 3e articulations phalangiennes des doigts susmentionnés. (Fig. 3).

L'examen radiographique des mains montre: partout structure des os nette et aiguë, mailles fines. Il est observé une halistérèse — le plus visiblement périarticulairement. Amincissement des scissures articulaires des articulations phalangiennes — partout de nature assez homogène. En outre, amincissement léger à la 1ère articulation phalangienne — le plus nettement au médus. Nodules de Héberden et de Bouchard. Aucune couche périostale, pas d'ostéophytes de traction. Aucune tuméfaction augmentée périarticulaire des parties molles. Il est possible que les scissures articulaires aux diverses cavités du poignet soient légèrement amincies. (signé: Niels Hansen). (Fig. 4).

*Épïcise:* Il s'agit d'une femme de 55 ans qui, après le commencement de la ménopause en 1929—30, souffre, depuis 1932, d'un goître augmentant se développant en 1940 à la maladie de Basedow. A mesure que sa maladie de Basedow se calme par traitement médicamenteux, une périarthrosis humeroscapularis duplex éclate, avec tuméfaction de la capsule et diminution de la mobilité des 2e et 3e articulations phalangiennes de l'index, du médus et de l'annulaire de la main *droite* et de l'index de la main *gauche*. La température a été subfébrile, sédimentation globulaire augmentée à 19 mm — mais la malade a été assez enrhumée. Les affections articulaires ne ressemblent ni à un rhumatisme chronique déformant, ni à une polyarthrite aiguë à un stade chronique (polyarthritidis chronica rheumatica), ni à un rhumatisme ostéo-articulaire.

3) ♂ (F. S. né 11/3—89) qui a souffert, depuis janvier 1942, de fatigue, nervosité, palpitations, tremblement des mains, perte de poids; métabolisme basal ambulants montrait 176—212 %. Après un court séjour au 7e service de l'Hôpital municipal de Copenhague, il est entré au service médical C. de l'hôpital de Bispebjerg du 27/5—42 jusqu'à septembre 1942 sous le diagnostic: Morbus Basedowii. *Objectivement:* Exophtalmie; glande thyroïde diffusément aggrandie. Stéthoscopie du cœur: naturel. Extré-



mités: naturelles. Par traitement médicale (alitement léger, diiodtyrosin et luminal) l'état général s'est amélioré; mais lorsqu'il est ensuite question d'opération, l'état s'aggrave, le métabolisme basal augmente à 147 → 185 %, le poids tombe et le pouls accélère; seulement après six semaines l'état se stabilisé par des doses augmentées de diiodtyrosin. Mi-juillet le malade se plaint de douleurs aux articulations des doigts; surtout à la main *droite*, ainsi qu'à la cheville *droite* et au genou *droit*; les douleurs disparaissent quand il remue les articulations. *Objectivement*: il n'est observé ni de chaleur, ni de rougeur, endolorissement ou gonflement des articulations. En même temps le malade commence à se plaindre d'intolérance à la chaleur — transpire beaucoup et fréquemment; il est traité sine effectu avec des pilules agaricines. La température est normale et la sédimentation globulaire qui a été (21/5) de 14 mm, est (29/6): 3 mm. Au cours du temps suivant les cas articulaires s'accroissent; le malade éprouve une sensation de gonflement, d'endolorissement et de diminution de la mobilité dans les 2e et 3e articulations phalangiennes de l'index, du médus et de l'annulaire de la main *droite* et dans les mêmes articulations de l'index et du médus de la main *gauche*. *Objectivement*: une tuméfaction endolorie de la capsule des articulations mentionnées est observée; pas de chaleur, ni de rougeur; diminution de la mobilité aux articulations mentionnées, de sorte qu'elles manquent de 1 cm à atteindre la paume; les articulations sont tenues volairement fléchies à un degré léger, mais peuvent être étendues. Pas de nodules de Héberden palpables; contracture débutante de Dupuytren de l'auriculaire *droit*. Aucun symptôme du côté des articulations des épaules et des coudes, où on trouve *objectivement*: mobilité libre sans endolorissement, ni de tuméfaction articulaire, Les autres articulations naturelles.

*L'examen radiographique* des articulations des doigts montre: aucune modification osseuse correspondant aux articulations. (signé: Ludvigsen).

*Épiscrise*: il s'agit d'un homme de 55 ans qui, pendant un hyperthyroïdisme surgi au printemps 1942 a, après un traitement médicamenteux pendant un peu plus de 2 mois, une tuméfaction de la capsule avec diminution de la mobilité dans les 2e et 3e articulations phalangiennes de l'index, du médus et de l'annulaire de la main *droite*, ainsi que de l'index et du médus de la main *gauche*. La température a été normale; la sédimentation globulaire a été normale. Ces affections articulaires ressemblent à celles trouvée temporairement chez des femmes pendant la ménopause, mais la tuméfaction de la capsule et le sexe du malade le contredisent; ils ne ressemblent pas au rhumatisme chronique déformant, ni à la polyarthrite aiguë à un stade chronique.

Il s'agit donc de 3 cas d'hyperthyroïdisme par suite de la maladie de Basedow — tous assez graves — pendant lesquels des symptômes articulaires se développent à l'index, au médus et à l'annu-

laire des deux mains; dans tous les 3 affections — dont les deux ont duré plus d'une dizaine d'années — les cas articulaires évoluent après une aggravation de l'état qui a été amélioré avant cette époque par un traitement médicamenteux. Les symptômes articulaires se montrent comme des douleurs persistantes, tuméfaction endolorie de la capsule et diminution de la mobilité — jusqu'à ankylose fibreuse — dans les 2<sup>e</sup> et 3<sup>e</sup> articulations phalangiennes des index, médius et annulaires; ils ne touchent en aucune façon la première articulation des doigts; les pouces ne sont que passagèrement atteints chez la plus malade. Les 2 cas dernièrement mentionnés semblent seulement en voie d'évoluer, tandis que le premier cas cité est entièrement développé et correspond aux cas référés dans la littérature; seulement, la nomenclature paraît être inexacte, puisque tous les 3 cas se montrent, tant du point de vue clinique que du point de vue radiologique, plutôt comme une arthrose — qui diffère toutefois des arthroses ordinaires par le fait qu'elle cause une «ankylose» fibreuse dans les articulations des doigts; l'ankylose osseuse ne s'observe qu'en cas de rhumatismes chroniques déformants — et d'affections articulaires suppuratives et tuberculeuses.

*Littérature:* Si l'on réunit les cas de connexité entre la maladie de Basedow et les maladies articulaires traités dans la littérature, on en trouve à peu près une centaine; comme il est dit ci-dessus, Perry a laissé entrevoir, en 1872, une certaine connexité entre la maladie de Basedow et la polyarthrite aiguë pendant les années suivantes jusqu'à 1909, Spender, Garrod, Vincent, Sargent, Levi & Rotschild et Spriggs traitent l'hypothèse qu'il doit être dû à une coïncidence plus qu'ordinaire que la polyarthrite et la maladie de Basedow apparaissent et évoluent en même temps. Vincent trouve ainsi un «signe thyroïdien» apparaissant sous forme de tuméfaction et d'endolorissement de la glande thyroïde par une polyarthrite aiguë.

En 1908 Williaminoff décrit 2 cas de «polyarthritidis progressiva thyreotoxica» correspondant tous les deux à ce qu'on appelle dans la nomenclature danoise: polyarthritidis chronica primaria progressiva; chez l'un des malades on trouve un hypothyroïdisme; le myxoedème et l'affection articulaire disparaissent par des doses de thyroïdine; l'autre malade souffre d'un struma adenomatosa avec des symptômes thyroïdiques; par thyroïdectomie le malade est entièrement guéri.

En 1909 R. L. Jones présente 14 cas de «rheumatoid arthritis» avec la maladie de Basedow — dans tous les cas il s'agit de femmes — ainsi que 6 cas — 4 femmes et 2 hommes — avec «rheumatoid arthritis» et «larved» maladie de Basedow. Il souligne en même temps que beaucoup des symptômes secondaires de la maladie de Basedow sont également relevés par un rhumatisme chronique déformant, tels que: pigmentation, oedèmes passagers, phénomènes vasomoteurs, taches chaudes et moites à la peau.

Pendant les années suivantes Falta, A. Kocher, Deusch, Umber, Curschmann, Thiroloux, Fink, Poncet, Nathan, Herzberg, Weissenbach, Leeser & Simson, Cohn—Wolpe et Ssamarin décrivent plusieurs cas isolés, puis Duncan écrit en 1932 un grand travail traitant ce sujet. Chez 298 malades souffrant d'hyperthyroïdisme il a trouvé une relation spéciale entre l'hyperthyroïdisme et l'apparition de symptômes articulaires chez  $85 = 29\%$ ; il y avait à la fois des modifications de polyarthrite et d'ostéo-arthrose dans les articulations. Chez ces malade souffrant de «exophthalmic goiter» il trouvait des douleurs articulaires rayonnants dans l'une ou les deux épaules; en outre, les poignets et toutes les articulations des doigts du même côté furent attaqués — l'attaque dépendant de la durée de la maladie. Elles ne pouvaient être améliorées par physiothérapie et développaient — si elles n'étaient pas traitées correctement — une atrophie dans les parties molles du joug des épaules avec abduction et rotation restreintes dans les articulations des épaules; les mouvements en avant et en arrière de ces articulations étaient naturels. Dans les articulations des mains et des doigts se développait un épaissement périarticulaire avec diminution de la mobilité et «glazed appearance» de la peau au niveau des articulations. Si ces malades étaient au contraire traités par thyroïdectomie, il fut, en général, constaté — dans les 48—72 heures après l'opération — une amélioration et une guérison complète de l'affection articulaire se produisant «d'une vitesse dramatique»

Dans les cas de Leeser & Simson on a constaté la maladie de Basedow avec des affections articulaires chez une mère et une fille, tandis qu'une autre fille ne souffrait que de la maladie de Basedow. Dans le cas de Tschilow — mentionné ci-dessus — on a également observé une hérédité familiale concernant la combinaison de ces 2 affections.

Pendant ces dernières années Monroe, Bach, Viersma, Kirstein

& Lövgren, Crotti, Jonsson et Tschilow se sont occupés du problème. Bach a ainsi 3 cas qui furent améliorés par thyroïdectomie; Crotti se prononce pour l'hypothèse que les douleurs musculaires et articulaires qui existent en cas d'hyperthyroïdisme sont dues à un hyperparathyroïdisme fonctionnel causé par l'hyperthyroïdisme; il en résulte une déminéralisation susceptible de causer une polyarthrite atrophique avec des contractures et une décalcification générale; Hench & Bauer éprouvent toutefois de graves doutes sur cet hyperparathyroïdisme fonctionnel provoqué.

Dans le cas de Tschilow — une juive de 26 ans qui, après une angine, a des douleurs et d'ankylose dans les articulations de la main et des doigts avec diminution de la mobilité dans les articulations des épaules; goitre depuis l'âge de 16 ans, qui, peu de temps avant l'apparition des symptômes articulaires, a évolué à une maladie de Basedow — il est trouvé, à l'examen radiographique comme dans les cas présents: amincissement des surfaces cartilagineuses des articulations phalangiennes et contours atrophiques des jointures.

Le fait que l'hyperthyroïdisme peut également être combiné avec des affections articulaires est montré par la maladie de Kaschin-Beck, décrite le mieux par Schipatschoff, par l'Osteochondrosis destruens thyreopriva de Nyfeldt et par le Rheumatismus thyreoprivus chronicus de Th. Kocher. Looser, Monroe et spécialement Viersma ont examiné ces cas; ils trouvent une certaine connexité entre les arthroses et le myxoedème.

Les examens du métabolisme basal chez 400 malades avec des affections articulaires chroniques montraient un état normal en 59 % des cas, subnormal en 24.3 % et  $>$  normal en 16.7 % des cas; le métabolisme basal subnormal était observé tant chez les malades souffrant de rhumatisme chronique déformant que chez les malades souffrant de rhumatisme ostéo-articulaire; toute fois, il y avait, parmi les 16.7 % de métabolismes basaux supranormaux, plus de malades du type polyarthrite que du type rhumatisme ostéo-articulaire. (Rawls et alii).

*Discussion.* Comme il a été exposé ci-dessus, il y avait lieu de croire que les 3 cas mentionnés pourraient être une maladie articulaire spéciale à la maladie de Basedow; elle ne ressemble en rien aux cas avec lesquels on serait d'abord disposé à les mettre en relation. Les 2 femmes sont arrivées au retour d'âge, l'une est entrée dans la

période de la ménopause, l'autre l'a terminée il y a une dizaine d'années; ces cas pourraient donc être des arthroses climatériques, mais, abstraction faite des nodules de Bouchard démontrable radiologiquement et, chez l'une, des nodules de Héberden palpables, les symptômes ne s'y accordent pas. Par les arthroses climatériques il est observé des douleurs vagues et un endolorissement accentué à la palpation dans toutes les articulations des doigts sans modifications objectives démontrables sous forme de tuméfaction de la capsule, chaleur ou rougeur des articulations. Les douleurs atteignent leur maximum le matin et disparaissent par fonction. L'état est passager — et pourra souvent être amené à une fin rapide par des doses d'espèces estrogènes. Dans ce cas-ci, stilboestrol n'a eu aucun effet aux symptômes articulaires (Snorrason).

Le rhumatisme chronique déformant commence par fièvre ou états subfébriles; la réaction de la sédimentation globulaire est augmentée; les cas articulaires commencent aux articulations métacarpo-phalangiennes pour gagner ensuite les autres articulations; une tuméfaction endolorie, assez vigoureuse, dans la capsule des articulations apparaît, spécialement dans les 1ères articulations phalangiennes de l'index et du médus, et dans les 2e et 3e articulations phalangiennes des 4 doigts cubitales; on peut observer de la chaleur aux articulations mentionnées. Au fur et à mesure que la maladie évolue, la main caractéristique est développée avec les doigts déviés ulnairement, fléchis aux 1ère et 3e articulations phalangiennes et étendus à la 2e articulation phalangienne; souvent ils ankylosent osseusement dans cette position. Ce cas-ci ne ressemble pas non plus aux cas mentionnés ci-dessus — il n'y a nulle part question d'une affection des articulations métacarpo-phalangiennes, de même que la température et la réaction de la sédimentation globulaire étaient normales. L'explication de Duncan, Jones et des autres auteurs de ces cas comme des rhumatismes chroniques déformants ne peut donc à peine être correcte — contre cette hypothèse parle également la guérison prompte par thyroïdectomie.

Les divers types articulaires sont reproduits schématiquement à la fig. 5.

En conséquence, il ne s'agit pas d'une polyarthrite aiguë à un stade chronique, puisqu'aucun des malades n'a eu ou bien n'avait, à l'examen, des signes d'une polyarthrite aiguë; les cas ne ressemblent pas non plus au «eosinophile Rheumatismus» de Bürger, malgré

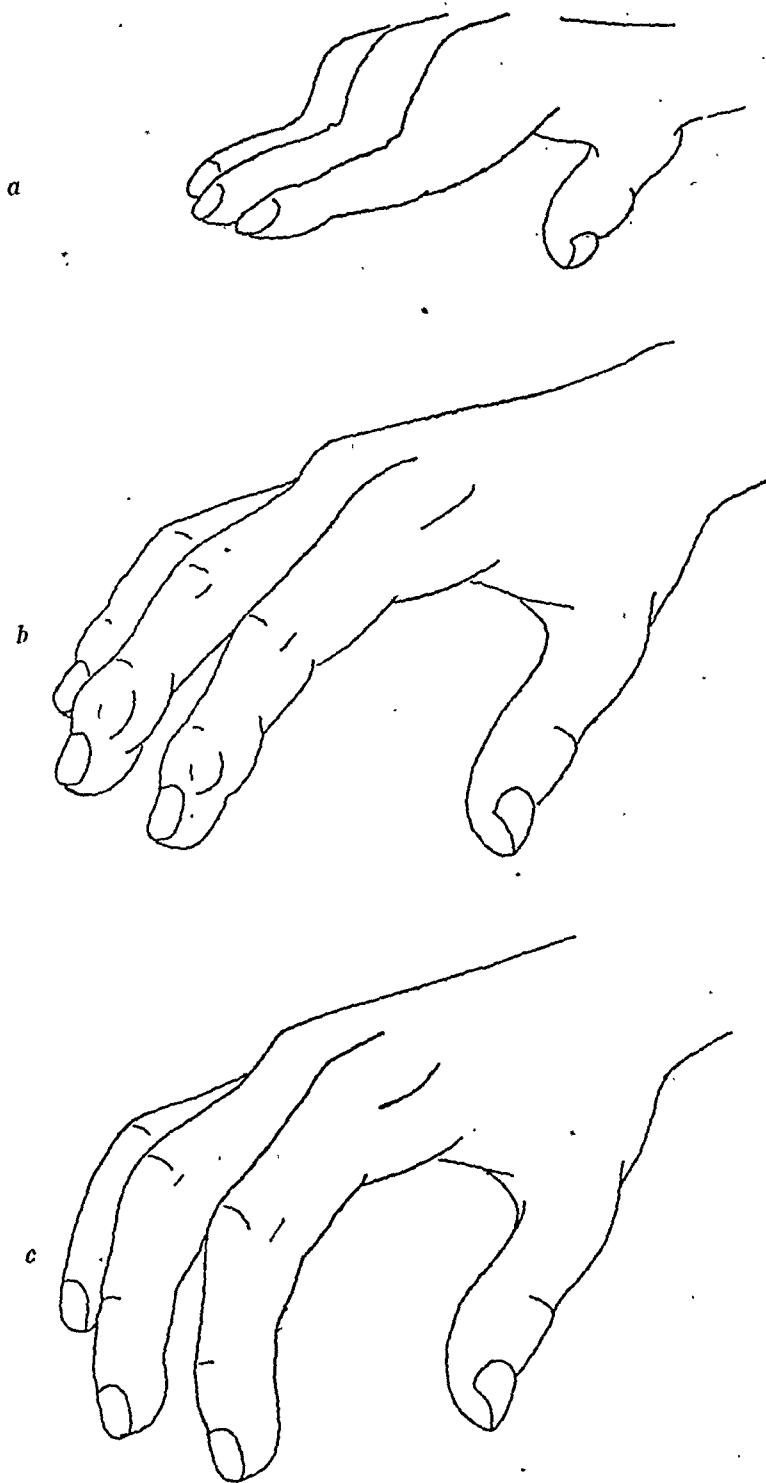


Fig. 5: Diverses déformités des doigts (schématiquement).

- a. Rhumatisme chronique déformant (polyarthritidis chronica primaria progressiva).
- b. Rhumatisme ostéo-articulaire (polyarthrosis) de la main avec nodules de Héberden.
- c. Maladie de Basedow (morbus Basedowii) avec symptômes articulaires.

le métabolisme basal augmenté, parce que l'hyperthyroïdisme est sans doute l'élément primaire de la maladie, et qu'on ne trouve ni cliniquement, ni d'un point de vue du sang, les conditions indiquées par Bürger (réaction augmentée de la sédimentation globulaire et eosinophilie vigoureuse).

Comme des causes éventuelles il faut certainement aussi écarter les traumatismes et la iodothérapie; aucun des malades ne montre des signes d'intoxication par l'iode; d'après Haenisch & Holthausen, la radiothérapie de la glande thyroïde ne donnera pas des symptômes articulaires aussi électifs.

Il faut remarquer que tous les 3 malades ont une contracture de Dupuytren débutante ou entièrement développée; ceci est sans doute dû à un hasard, mais, d'autre part, elle ne peut être la cause des symptômes des doigts, parce que la contracture de Dupuytren ne dépasse que dans des cas extrêmement rares l'annulaire et l'auriculaire. Ghormley ne mentionne nulle part l'hyperthyroïdisme comme la cause d'une contracture de Dupuytren — les traumatismes et l'hérédité doivent en être les facteurs étiologiques les plus essentiels.

Williaminoff, Deusch, Curschmann et Duncan sont d'avis que les affections musculaires et articulaires mentionnées — qui sont toutefois si graves qu'elles engendrent des ankyloses fibreuses avec dégénération cartilagineuse consécutive (les cavités articulaires dont l'amincissement est démontrable radiographiquement) — devraient être des troubles trophiques, correspondant aux atrophies de la peau et des muscles qui ne font presque jamais défaut à l'hyperthyroïdisme par suite de troubles du système nerveux végétatif. Ceci correspond à la théorie soutenue par Charcot concernant la genèse par la voie neurogène des rhumatismes chroniques déformants symétriques qui trouve un appui si fort dans les arthropathies par tabes dorsal et syringomyélie. Tout l'aspect clinique de l'affection et sa disparition qui se fait «d'une vitesse dramatique» par thyroïdectomie témoignent aussi dans le même sens. L'arthrose développée dans les articulations est certainement plutôt due à l'inactivité articulaire survenue par suite de l'ankylose fibreuse qu'elle est un symptôme direct de l'hyperthyroïdisme. La théorie de Jones et d'autres auteurs de l'affection articulaire comme un «rhumatoïd arthritis» est, d'après les cas mentionnés ici, à peine exacte — une polyarthrite ne pourrait jamais se montrer aussi

transitaire qu'elle est décrite par l'auteur lui-même; ce n'est que la nomenclature qui a fait défaut.

Le fait que tous les 3 malades ont la contracture de Dupuytren est peut-être plutôt une coïncidence qu'une suite de l'hyperthyroïdisme, même si ceci pourrait aussi très bien s'adapter à la théorie de Charcot.

Comme référé dans la littérature, le pronostic de l'affection est mauvais, puisque les cas dans les doigts évolueront à l'ankylose, tandis que les symptômes dans les épaules donneront des douleurs continues, à moins que le malade ne soit traité radicalement à temps. Dans le premier des 3 cas mentionnés ci-dessus, la radiothérapie n'a pas eu le temps d'avoir de l'effet, mais il faut bien espérer qu'elle l'aura dans les deux autres cas.

### Résumé.

Il s'agit de 3 cas d'hyperthyroïdisme, où, concurremment avec une aggravation de la maladie, on a observé des symptômes articulaires spécifiques avec développement d'ankylose fibreuse dans les 2e et 3e articulations phalangiennes de l'index, du médius et de l'annulaire, ainsi que, dans les deux cas, une periarthrosis humero-scapularis duplex, peut-être spécifique elle aussi.

### Littérature.

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From Department II, the Municipal Hospital, Copenhagen (Chief: Professor H. J. Bing, M. D.; later, H. Heckscher, M. D.) and Dep. A, the General Laboratory of National Health Insurance Physicians (Chief: K. Brochner-Mortensen, M. D.)

## **Iron content of the serum in patients with hemorrhagic anemia.\***

By

**KNUD BRØCHNER-MORTENSEN.**

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In patients with hemorrhagic anemia a considerable decrease in the iron content of the serum has been observed by many investigators (1, 2, 5, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21).

After an acute loss of blood the values for serum iron soon begin to fall. After venesection a conspicuous decrease is noted within a few hours (16). On hemorrhage at parturition the value falls considerably within a few minutes (1) but here the conditions are more complicated, as other factors besides the hemorrhage itself cannot be excluded with certainty.

In some cases a transitory rise in serum iron up to a high normal or definitively increased level has been observed about one day after the hemorrhage (10, 11, 14, 16). Then the serum iron decreases for some length of time, the lowest values being often reached after some days, sometimes later (10, 13, 16).

In some cases very low values are observed, even lower than 10  $\gamma$  %.

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During the regeneration of the blood the serum iron values keep at a low level, rising again to normal only when the the hemoglobin has been regenerated essentially (10, 16).

Venesection with evacuation of about 500 cm<sup>3</sup> of blood gives regularly a marked decrease in serum iron, which as a rule returns rapidly to normal values (10, 16).

Examination of »professional» donors of blood for transfusion shows most often normal values for serum iron, but in some cases protracted decrease even in the absence of anemia (15, 16, 17).

In chronic hemorrhagic anemia the values for serum iron are permanently low (10, 13, 16).

Under iron treatment of patients with hemorrhagic anemia the serum iron sometimes shows a moderate rise, but then it falls off again if the iron treatment is discontinued before full regeneration of the blood (1, 10).

### *Writer's Investigations.*

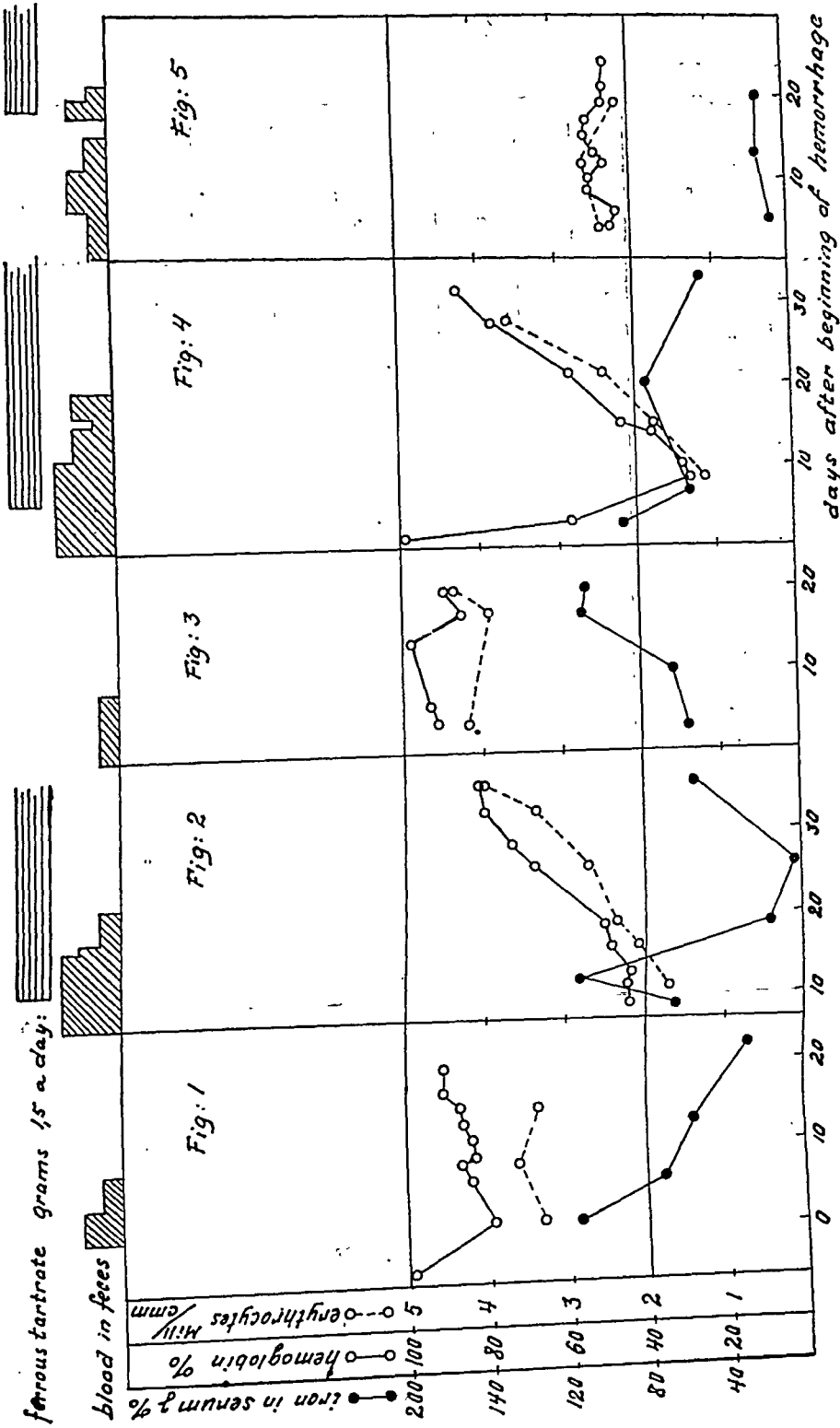
#### *Material.*

The iron content of the serum was examined in 22 patients with more or less pronounced hemorrhagic anemia, including 18 with bleeding from peptic ulcers of the stomach or duodenum, 1 with bleeding from oesophageal varices (No. 2), 1 with epistaxis in scurvy (No. 18), and 2 with uterine bleeding (Nos. 15 and 16). Of these patients 21 were admitted to Deep. II of the Municipal Hospital, and they represent an accidental selection of patients with hemorrhagic anemia admitted within the period of 1940—42. One patient was admitted to Dep. B of the Bispebjerg Hospital, and I wish here to acknowledge my indebtedness to the chief of this department, Professor E. Meulengracht, M. D., for kind permission to perform the examination.

#### *Technique.*

The iron content of the serum has been determined after the method given by Bröchner-Mortensen & Olsen (4).

The hemoglobin content of the blood was determined on hydrochloric acid hematin in Autenrieth's colorimeter, adjusted after Haldane's standard (100 % hemoglobin = 18.5 vol. % oxygen capacity).



Figs. 1—5. Variations in the iron content of the serum in patients with hemorrhagic anemia.

The lowest values for serum iron were most often found after some length of time had passed after the hemorrhage — only in a few cases within the first week after the commencement of the bleeding, more often after from one to several weeks.

In a couple of patients the variations in serum iron were followed from the very beginning of the hemorrhage, and here the obtained values were normal during the first 24 hours, whereafter they were falling off. An example of this is shown in Fig. 1.

Patient No. 13 was a man, 34 years old, who for 8 years had had symptoms of duodenal ulcer (verified on roentgenography). On admission, no blood was found in the feces. A few days later, however, melæna appeared, and at the same time the hemoglobin percentage fell from 99 to 79 %. In the morning after the commencement of the bleeding the serum contained 112  $\gamma$  % iron; after this, the values kept falling slowly to 38  $\gamma$  %, on the 22nd day.

The transitory secondary rise in serum iron mentioned by several previous authors was observed in 3 of these patients. An example of this is given in Fig. 2.

Patient No. 22 was a man, aged 44, who for 5—6 years had had symptoms of gastric ulcer, and melæna several times, the last time 7 days before admission.

On the day after admission he showed 64  $\gamma$  % serum iron, 4 days later 113  $\gamma$  %; after this, the values fell to 4  $\gamma$  %, 26 days after the commencement of the bleeding.

On the whole there was only slight correlation between the values for serum iron and hemoglobin, and the variations in the two were not parallel.

In patients No. 4 (Fig. 3) and No. 10 (Fig. 4) the minimum values obtained for serum iron are of the same magnitude, although the loss of blood in one case was very slight, in the other very great.

Patient No. 4 was a man, aged 55, who for several years had had symptoms of duodenal ulcer. On the day of admission he had a moderate hematemesis, but after a few days the stools were free from blood, and the hemoglobin percentage did not fall below 85. The first examination, 3 days after the hematemesis, showed a serum iron content of 59  $\gamma$  %; and as early as on the 17th day it was normal again, 110  $\gamma$  %.

Patient No. 10 was a man, 25 years old, who had had gastric ulcer for 3 years. On the day of admission he had several large hematemeses. The hemoglobin percentage fell from 99 to 27, but under iron treatment it rose

rapidly again, from 29 to 85 in 21 days. As long as 3 days after the commencement of the bleeding the iron content of the serum was still 87  $\gamma$  %; and after this it kept at a subnormal level. The lowest value (48  $\gamma$  %) was observed 33 days after the bleeding.

Generally the serum iron content keeps at a low level till the blood regeneration is practically completed or even for some time after this. But this rule is not without exceptions.

Among 5 patients who at the end of the examination showed 90–99 % hemoglobin, 4 gave normal values for serum iron (91–154  $\gamma$  %), while in 1 the value was considerably decreased (30  $\gamma$  %). In 5 patients with 80–89 % hemoglobin, the serum iron content was between 24 and 65  $\gamma$  %.

In patients with less than 80 % hemoglobin, low values for serum iron were found in some cases; still, normal values for serum iron (95 and 119  $\gamma$  %) were observed in 2 patients with a hemoglobin percentage of 72 and 79, respectively.

Fairly large and protracted hemorrhage is associated with permanent low values for serum iron (Fig. 5).

Patient No. 21 was a man, 70 years old, who for 10 years had had symptoms of duodenal ulcer. About 6 weeks before admission he had had melæna for 8 days. Melæna was present again on the day of admission; and the bleeding continued throughout the observation period. Roentgenography showed an ulcer of the duodenum. On the 5th day after the commencement of the bleeding the iron content of the serum was 8  $\gamma$  %, and it kept at an excessively low level. The hemoglobin percentage was constantly between 44 and 51.

In 5 patients the serum iron content was determined before intake of 1 g of ferrous lactate, and also 2 and 4 hours after (Table 2, Fig. 6).

For control material, altogether 17 tests of this kind were performed on 15 experimental subjects:

I: 7 patients with myalgia, chronic constipation, enuresis, etc., whose iron metabolism must be assumed to be normal, and in whom the Ewald test meal showed normochyilia.

II. 3 patients with normochylic gastritis. The diagnosis was verified by gastroscopy. In each case the feces were free from blood.

III. 5 patients with achylia-hypochyilia (free acid: 0).

In the patients without any stomach lesion (Group I) the iron content of the serum prior to the intake of iron was normal (87—182  $\gamma$  %).

One patient, who was very nauseated during this experiment, showed no definitely measurable rise in serum iron after the administration of iron. Repeated intake of iron was followed by a rise of 52  $\gamma$  % in 2 hours.

In another patient a maximal rise of 49  $\gamma$  % was observed, in 2 patients a rise between 50 and 100  $\gamma$  %, and in 3 a rise between 100 and 150  $\gamma$  %. The greatest rise observed was 148  $\gamma$  %, and the highest absolute value observed after the intake of iron was 254  $\gamma$  %.

In 5 tests the highest value for serum iron was obtained after 2 hours, in 3 tests after 4 hours.

In the 3 patients with normochylic gastritis (Group II) the values for serum iron prior to the test were normal (106—121  $\gamma$  %) and after the intake of iron there was a rise of 33—111  $\gamma$  %, with 232  $\gamma$  % as maximum value.

In 4 of the 5 patients with achylia-hypochylia (Group III) the serum iron was found to be normal prior to the test (117—194  $\gamma$  %) and after the intake of iron there was a rise of 80—94  $\gamma$  %, the highest value being 277  $\gamma$  %.

The fifth patient with achylia was a woman, aged 45, who had been under treatment for simple achylic anemia. On the day of the test her hemoglobin percentage was 95. Prior to the test she showed a distinct decrease in serum iron. The intake of iron was followed by a very high rise of 259  $\gamma$  % to the level of 318  $\gamma$  %, presumably expressing an increased want of iron.

So the total result of these tests on the control material was quite in harmony with previous experiences, showing that the gastric acidity has no measurable influence on the iron tolerance curves after intake of soluble ferrous salts, and that the height of the individual tolerance curves is subject to great variations.

In 4 tests the patients took the ordinary diet; in 9 tests the patients were fasting for 2 hours after the intake of iron; and in 4 tests they were fasting for 4 hours. These variations in the technique of the tests had apparently no influence on the tolerance curve.

Of the 5 patients with hemorrhagic anemia on whom this test was carried out, one (No. 11) showed no measurable rise in serum iron 4

Table  
Iron Content of the Serum before and after Ingestion of 1 g. of Ferrous

| Stomach func-<br>Ewald's                    |                      |  |     |              |              |              |                           |               |
|---|----------------------|--|-----|--------------|--------------|--------------|---------------------------|---------------|
| Pt.<br>No.                                  | Dep. Case<br>Records | Diagnosis  | Sex | Age<br>years | Height<br>cm | Weight<br>kg | Amount<br>cm <sup>3</sup> | Günz-<br>burg |
| A. Control Material.                        |                      |  |     |              |              |              |                           |               |
| I. Patients with Normochylia.               |                      |  |     |              |              |              |                           |               |
| 1   | II 1334/42           | Mental depression, psychogenic   | M.  | 29           | 186          | 83           | 30+10                     | +             |
| 2   | II 1250/42           | Enuresis.  | F.  | 16           | 159          | 49           | 48+ 9                     | +             |
| 3   | II 1254/42           | Chronic constipation   | M.  | 41           | 166          | 61           | 65+14                     | +             |
| 4   | II 1354/42           | Chronic constipation   | M.  | 33           | 162          | 57           | 77+31                     | +             |
| 5   | II 1404/42           | Obesity; Myalgia   | F.  | 52           | 169          | 75           | 75+17                     | +             |
| 6   | II 1327/42           | Obesity; Myalgia   | F.  | 45           | 160          | 67           | 5+10                      | +             |
| 7   | II 1449/42           | Myalgia  | F.  | 50           | 151          | 77           | 38+ 9                     | +             |
| II. Patients with Normochylic<br>Gastritis. |                      |  |     |              |              |              |                           |               |
| 8   | II 1308/42           | Gastritis, slight degree.  | M.  | 56           | 162          | 51           | 42+12                     | +             |
| 9   | II 1453/42           | Gastritis  | M.  | 35           | 181          | 72           | 90+65                     | +             |
| 10  | II 1310/42           | Gastritis  | M.  | 41           | 177          | 57           | 70+54                     | +             |
| III. Patents with Achylia or<br>Hypochylia. |                      |  |     |              |              |              |                           |               |
| 11  | II 123-5/41          | Gastric achylia  | M.  | 31           | —            | 53           | 5                         | —             |
| 12  | II 1323/42           | Gastric hypochylia;<br>Gastritis   | M.  | 42           | 174          | 72           | 5+11                      | 0             |
| 13  | II 99—3/41           | Gastric achylia;<br>Constipation   | F.  | 45           | —            | —            | 44—46                     | —             |
| 14  | II 1392/42           | Gastric hypochylia;<br>Obesity;<br>Various myoses.                         | F.  | 50           | 166          | 88           | 15—13                     | 0             |
| 15  | II 1247/42           | Gastric achylia;<br>Simple achylic anemia (previous)                       | F.  | 45           | 158          | 66           | 2                         | —             |
| B. Patients with Hemorrhagic<br>Anemia.     |                      |  |     |              |              |              |                           |               |
| 5   | II 1596/42           | Ulcer of stomach;<br>Hematemasis   | M.  | 48           | 176          | 64           | 28+37                     | 0             |
| 3   | II 21-6/41           | Juxtapyloric ulcer;<br>Hematemesis; Melæna.                                | F.  | 48           | 151          | 42           | 41+ 8                     | —             |
| 7   | II 74-6/41           | Juxtapyloric ulcer; Melæna   | M.  | 34           | —            | 51           | 68—24                     | —             |
| 11  | II 1495/42           | Juxtapyloric ulcer (?);<br>Cirrhosis of liver (?);<br>Hematemesis; Melæna. | M.  | 59           | 166          | 64           | 30+27                     | 0             |
| 19  | BBH-B-111/42         | Juxtapyloric ulcer (?); Melæna   | F.  | 19           | —            | —            | 60+12                     | —             |

2.

Lactate in Patients with Hemorrhagic Anemia and in Control Material.

| Lactate measured by test meal |                              | Hemoglobin percent | Sedimentation test mm/hr | Temperature | Serum iron $\gamma$ %   |                  |      |                   |       | Fasting after intake of iron in hours | Days after onset of hemorrhage |
|-------------------------------|------------------------------|--------------------|--------------------------|-------------|-------------------------|------------------|------|-------------------|-------|---------------------------------------|--------------------------------|
| free acid (Kongo)             | total acid (Phenolphthalein) |                    |                          |             | I Before intake of iron | II 2 hours after |      | III 4 hours after |       |                                       |                                |
|                               |                              |                    |                          |             |                         | abs. value       | II—I | abs. value        | III—I |                                       |                                |
| 30                            | 60                           | 105                | 4                        | 0           | 182                     | 191              | + 9  | 183               | + 1   | 2                                     | —                              |
|                               |                              |                    |                          |             | 132                     | 185              | + 53 | —                 | —     | 0                                     | —                              |
| 43                            | 76                           | 94                 | 9                        | 0           | 156                     | 177              | + 21 | 247               | + 91  | 4                                     | —                              |
|                               |                              |                    |                          |             | 140                     | 204              | + 64 | 177               | + 33  | 0                                     | —                              |
| 34                            | 65                           | 106                | 5                        | 0           | 126                     | 145              | + 19 | 175               | + 49  | 4                                     | —                              |
| 60                            | 85                           | 98                 | 2                        | 0           | 111                     | 233              | +122 | 218               | +107  | 2                                     | —                              |
| 36                            | 60                           | 98                 | 9                        | 0           | 110                     | 139              | + 29 | 190               | + 80  | 2                                     | —                              |
| (40)                          | (90)                         | 91                 | 5                        | 0           | 106                     | 254              | +148 | 211               | +105  | 4                                     | —                              |
| 40                            | 72                           | 88                 | 11                       | 0           | 87                      | 195              | +108 | 194               | +107  | 2                                     | —                              |
| 34                            | 74                           | 107                | 2                        | 0           | 121                     | 232              | +111 | 187               | + 66  | 2                                     | —                              |
| 38                            | 68                           | 105                | 5                        | 0           | 121                     | 154              | + 33 | 152               | + 31  | 2                                     | —                              |
| 37                            | 78                           | 89                 | 6                        | 0           | 106                     | 163              | + 57 | 193               | + 87  | 2                                     | —                              |
| 0                             | —                            | 102                | 1                        | 0           | 194                     | 277              | + 83 | 275               | + 81  | 0                                     | —                              |
| 0                             | (28)                         | 105                | 2                        | 0           | 170                     | 218              | + 48 | 250               | + 80  | 4                                     | —                              |
| 0                             | 15                           | 86                 | 13                       | 0           | 151                     | 231              | + 80 | 218               | + 67  | 0                                     | —                              |
| 0                             | 24                           | 94                 | 2                        | 0           | 117                     | 211              | + 94 | 188               | + 71  | 2                                     | —                              |
| 0                             | —                            | 95                 | 3                        | 0           | 59                      | 318              | +259 | 283               | +224  | 2                                     | —                              |
| 4                             | 45                           | 78                 | 8                        | 0           | 66                      | 101              | + 35 | 61                | — 5   | 2                                     | 3                              |
| 52                            | 82                           | 68                 | 5                        | 0           | 59                      | 277              | +218 | 232               | +173  | 0                                     | 15                             |
| 21                            | 67                           | 40                 | 45                       | 0           | 50                      | 268              | +218 | 326               | +276  | 0                                     | 12                             |
| 0                             | 24                           | 27                 | 30                       | 0           | 46                      | 48               | + 2  | 44                | — 2   | 2                                     | 4                              |
| 27                            | 52                           | 59                 | 10                       | 0           | 46                      | 116              | + 70 | 106               | + 60  | 1                                     | 10                             |
|                               |                              | 47                 | 7                        | 0           | 28                      | —                | —    | 412               | +384  | 0                                     | 30                             |



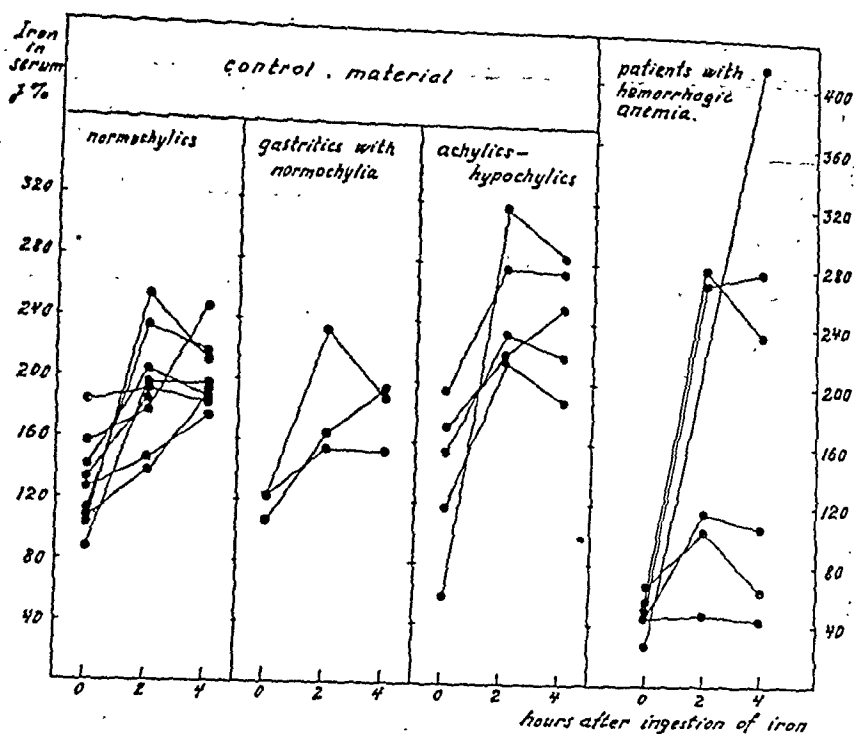


Fig. 6. Iron content of the serum before and after ingestion of 1 g of ferrous lactate in patients with hemorrhagic anemia and in a control material.

days after the beginning of the hemorrhage; on repetition of the test (6 days later) there was a rise of 70  $\gamma$  %.

In another patient (No. 5) on whom the test was performed 3 days after the commencement of the bleeding, there was a slight rise in serum iron (35  $\gamma$  %).

Two patients (Nos. 3 and 7), on whom the test was performed respectively 15 and 12 days after the beginning of the hemorrhage, showed a great increase in serum iron (218  $\gamma$  %) to the respective values of 277 and 268  $\gamma$  %.

Finally, one patient (No. 19) in whom the bleeding presumably had lasted about one month or more responded to the test with a very considerable rise in serum iron, from 28 to 412  $\gamma$  %.

This patient was a woman, 19 years old, who for about one month had had symptoms of anemia increasing in intensity. On admission she showed: Hemoglobin 39 %; red blood count 2.71 million; color index 0.67. The feces presented a moderate degree of melæna, which ceased shortly after the admission, and the cause of which was not demonstrated.

Thus 3 out of the 5 patients showed on this test a greater rise in serum iron than was observed in the control material. This rise was greatest in those patients on whom the test was performed a relatively long time after the beginning of the hemorrhage, but apparently was not dependent on the simultaneous hemoglobin value.

On 5 of the patients with hemorrhagic anemia determination of the serum iron was made before and after intravenous administration of 10 mg of iron as ferrous lactate (Table 3, Fig. 7).

For control material 10 similar tests were made on 10 persons whose iron metabolism must be assumed to have been normal.

In the control material, 5 minutes after the injection there was a rise in serum iron between 157 and 333  $\gamma$  % to values of 283—453  $\gamma$  %. 60 minutes after the injection there was a fall of 30—108  $\gamma$  % (averaging 60  $\gamma$  %) or 18—38 % (averaging 28 %) of the increase. 120 minutes after the injection, 5 of the experimental subjects showed a fall of 52—106  $\gamma$  %, (averaging 83  $\gamma$  %) or 31—60 % (averaging 42 %) of the increase.

Patients with hemorrhagic anemia showed 5 minutes after the injection a rise in serum iron of 172—338  $\gamma$  % to values of 226—354  $\gamma$  %. 60 minutes after the injection there was a fall of 48—109  $\gamma$  % (averaging 68  $\gamma$  %) or 26—41 % (averaging 32 %) of the increase, 120 minutes after the injection, 4 of the patients showed a fall of 79—131  $\gamma$  % (averaging 100  $\gamma$  %) or 42—61 % (averaging 52 %) of the increase.

So in the test with intravenous administration of iron the patients with hemorrhagic anemia showed no definite deviation from the control material.

### Discussion.

The present studies on 22 patients with hemorrhagic anemia have in every instance shown a decrease in serum iron, most often in a considerable degree, which is quite in harmony with previous experiences.

Most likely, this decrease is attributable to the increased consumption of iron in the regeneration of hemoglobin. This view finds support in the fact that some authors (10, 16), have found

Table

*Iron Content of the Serum before and after Intravenous Injection of 10 mg of Iron as*

| Pt. No.                                     | Dep. Case Records | Diagnosis   | Sex | Age years | Height cm | Weight kg | Hemoglobin per cent |
|---|-------------------|---|-----|-----------|-----------|-----------|---------------------|
| <i>A. Control Material.</i>                 |                   |   |     |           |           |           |                     |
| 1   | II 873/42         | Chronic constipation  | F.  | 19        | 174       | 66        | 98                  |
| 2   | II 481/42         | Nil   | M.  | 25        | 169       | 57        | 103                 |
| 3   | II 448/42         | Myalgia   | M.  | 29        | 179       | 78        | 93                  |
| 4   | II 436/42         | Gastritis, slight degree  | M.  | 38        | 164       | 60        | 102                 |
| 5   | II 1339/42        | Myalgia   | M.  | 44        | 160       | 61        | 113                 |
| 6   | II 1274/42        | Myalgia   | F.  | 30        | 165       | 59        | 85                  |
| 7   | II 498/42         | Fissura ani   | M.  | 20        | 176       | 72        | 100                 |
| 8   | II 432/42         | Proctitis, slight degree  | M.  | 47        | 154       | 53        | 108                 |
| 9   | II 783/42         | Neurasthenia  | M.  | 49        | 174       | 69        | 95                  |
| 10  | II 832/42         | Observation for duodenal ulcer  | M.  | 20        | 179       | 67        | 110                 |
| <i>B. Patients with Hemorrhagic Anemia.</i> |                   |   |     |           |           |           |                     |
| 2   | II 1358/42        | Cirrhosis of liver;<br>Hematemesis  | M.  | 59        | 173       | 71        | 85                  |
| 1   | II 976/42         | Ulcer of stomach;<br>Hematemesis  | M.  | 48        | 170       | 78        | 65                  |
| 11  | II 1495/42        | Juxtapyloric ulcer (?);<br>Cirrhosis of liver (?);<br>Hematemesis; Melæna | M.  | 59        | 166       | 64        | 27                  |
| 5   | II 1596/42        | Ulcer of stomach;<br>Hematemesis  | M.  | 48        | 176       | 64        | 78                  |
| 19  | BBH-B-111/42      | Juxtapyloric ulcer (?)<br>Melæna  | F.  | 19        | —         | —         | 47                  |

<sup>1</sup> Temperature level

0 = normal temperature

I = subfebrile temperature (< 38° C).

normal or merely slightly subnormal values for serum iron after hemorrhage in patients with aplastic anemia, presumably because the bone marrow has not been capable of increased regeneration. It must be mentioned, however, that no information is given about the serum iron level of these patients prior to the hemorrhage.

## 3.

*Ferrous Lactate in Patients with Hemorrhagic Anemia and in a Control Material.*

| Sedimentation<br>reaction mm/1 hr | Temperature<br>level 1 | Before<br>injection | Serum iron $\gamma$ %     |      |               |                            |     |               |                             |     |           | Days after<br>onset of<br>hemorrhage |
|-----------------------------------|------------------------|---------------------|---------------------------|------|---------------|----------------------------|-----|---------------|-----------------------------|-----|-----------|--------------------------------------|
|                                   |                        |                     | 5 min. after<br>injection |      |               | 60 min. after<br>injection |     |               | 120 min. after<br>injection |     |           |                                      |
|                                   |                        |                     | Abs.<br>value             | Rise | Abs.<br>value | Fall                       |     | Abs.<br>value | Fall                        |     |           |                                      |
|                                   |                        |                     |                           |      |               | Abs.                       | %   |               | Abs.                        | %   |           |                                      |
| 3                                 | 0                      | 179                 | 377                       | +198 | 309           | — 68                       | —34 | 282           | — 95                        | —48 | —         |                                      |
| 2                                 | 0                      | 178                 | 440                       | +262 | 370           | — 70                       | —27 | —             | —                           | —   | —         |                                      |
| 2                                 | 0                      | 176                 | 342                       | +166 | 298           | — 44                       | —26 | —             | —                           | —   | —         |                                      |
| 3                                 | 0                      | 165                 | 378                       | +213 | 287           | — 91                       | —38 | —             | —                           | —   | —         |                                      |
| 2                                 | 0                      | 152                 | 318                       | +166 | 286           | — 32                       | —19 | 266           | — 52                        | —31 | —         |                                      |
| 4                                 | 0                      | 145                 | 326                       | +181 | 252           | — 74                       | —41 | 220           | —108                        | —60 | —         |                                      |
| 2                                 | 0                      | 125                 | 282                       | +157 | 252           | — 30                       | —19 | —             | —                           | —   | —         |                                      |
| 3                                 | 0                      | 120                 | 453                       | +333 | 345           | —108                       | —32 | —             | —                           | —   | —         |                                      |
| 4                                 | 0                      | 113                 | 323                       | +210 | 277           | — 46                       | —22 | 246           | — 77                        | —37 | —         |                                      |
| 5                                 | 0                      | 100                 | 354                       | +254 | 308           | — 46                       | —18 | 265           | — 89                        | —35 | —         |                                      |
| 37                                | 0                      | 135                 | 326                       | +191 | 268           | — 58                       | —30 | 220           | —106                        | —55 | 2         |                                      |
| 13                                | I                      | 73                  | 260                       | +187 | 212           | — 48                       | —26 | 181           | — 79                        | —42 | 11        |                                      |
| 30                                | 0                      | 63                  | 238                       | +175 | 167           | — 71                       | —41 | 107           | —131                        | —61 | 9         |                                      |
| 8                                 | 0                      | 54                  | 226                       | +172 | 174           | — 52                       | —30 | 141           | — 85                        | —49 | 4         |                                      |
| 7                                 | 0                      | 16                  | 354                       | +338 | 245           | —109                       | —32 | —             | —                           | —   | $\geq 30$ |                                      |

Possibly the deterioration of the red blood cells in these patients is less than usual, and this may have been a contributory cause of the low values for serum iron after an acute hemorrhage. Still, a change in the deterioration of the red blood cells and in the liberation of iron associated herewith is hardly marked enough to have

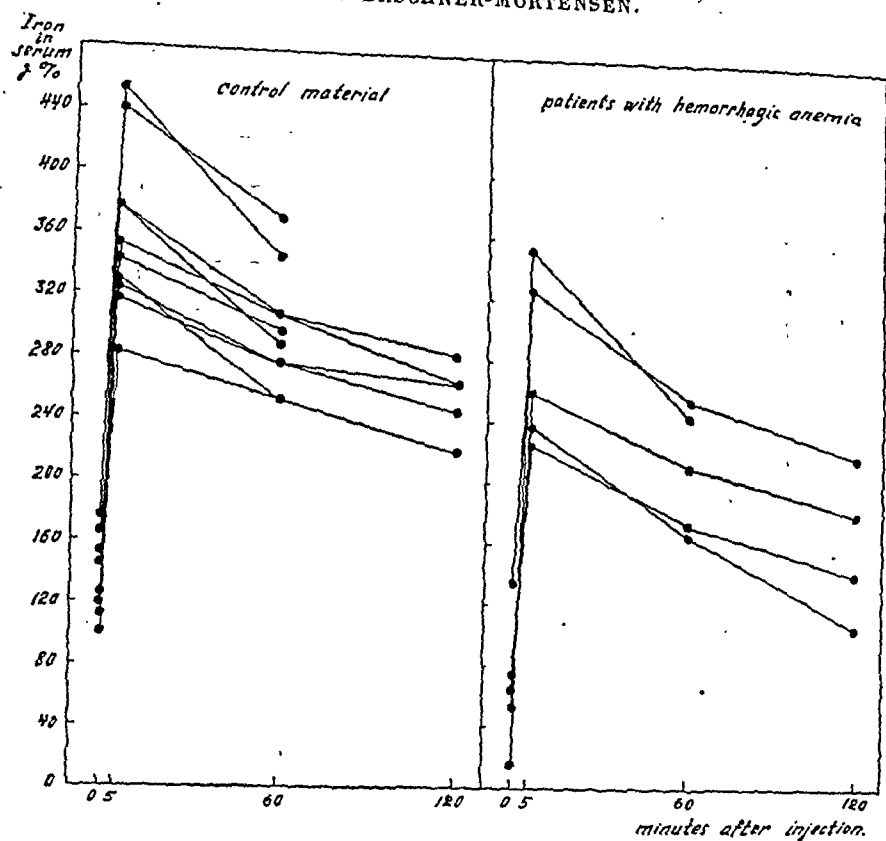


Fig. 7. Iron content of the serum before and after intravenous injection of 10 mg of iron as ferrous lactate in patients with hemorrhagic anemia and in a control material.

any essential influence on the serum iron content (10), and in chronic hemorrhagic anemia the deterioration of red blood cells appears rather to be increased (10).

The cause of the low values for serum iron after bleeding is not to be looked for in dilution of the plasma, as the fall in serum iron most often is considerably greater than the decrease in the red blood count, even though the tissue juice which is flowing into the blood stream may hardly be assumed to be free from iron. Furthermore, the variations in the serum iron content and the red blood count are not parallel.

There has been a certain tendency to look upon the low values for serum iron as signifying iron deficiency. In acute hemorrhage, however, a true iron deficiency will usually be out of the question, as the previously normal depots of the organism should be able to cover the loss of iron associated with a hemorrhage of 2—3 liters (3).

This is in agreement with the general clinical experience, that a patient with acute hemorrhagic anemia is able to reproduce his normal hemoglobin percentage from values a little below 50 % without any medicamental supply of iron, even if his diet is poor in iron. This will require exactly the 1.5 g of iron assumed to be present in the depots.

So the low values for serum iron are not to be taken generally as expressions of an iron deficiency proper, but merely as resulting from a certain lagging in the liberation of iron from the depots in proportion to the iron consumption of the bone marrow. Only in great or repeated hemorrhages, or in patients with small iron depots may a true iron deficiency be involved.

The transitory rise in serum iron shortly after the hemorrhage that has been observed in this material, as well as by previous authors (10, 11, 14, 16), is usually to be interpreted as resulting from a sudden mobilization of iron from the depots. But as yet we know nothing definite about this.

The present studies agree with previous experiences in the observation that the serum iron in such cases most often keeps at a low level till the hemoglobin regeneration is completed essentially, and in several cases even for some additional length of time, perhaps till the depots are replenished.

The low values for serum iron have to be taken as an expression of a wanting balance in the internal iron metabolism. It seems rational, therefore, to continue with the iron treatment at any rate till the serum iron becomes normal, in order to reestablish the physiological balance as soon as possible, especially in patients who have had a more profuse or protracted hemorrhage and in patients whose iron absorption is inhibited by achylia or similar morbid conditions.

After the loss of iron through hemorrhage the external iron metabolism is altered in a compensatory direction. Regardless whether we accept the modern view, that the normal adult organism absorbs or excretes measurable amounts of iron only under special conditions, we have to consider it definitively established that a loss of iron from hemorrhage, is followed by a retention of iron by the organism [cf. previous survey (3)].

The increased demand of the organism for iron during the increased blood regeneration has been observed by previous investi-

gators (7, 8, 10) on peroral administration of iron as expressed by a greater rise in serum iron in patients with hemorrhagic anemia than in normal subjects. Something similar was observed in 3 of the patients here examined on intake of iron 12—30 days after the commencement of the bleeding, whereas the rise in serum iron was lower or absent in 3 such tests performed on 2 patients 3—10 days after the onset of the hemorrhage.

This difference in the height of the iron tolerance curves might possibly be explained as attributable to the circumstance that the marked increase in hemoglobin formation and the resulting increase in iron requirement took place but gradually. If this be the case it will also explain why the fall in serum iron is relatively slow in the first period after the bleeding, and why the lowest values for serum iron most often are observed only after some length of time.

The low iron tolerance curves observed shortly after the hemorrhage need not signify a deficient absorption, however; they might also result from a very rapid removal of the absorbed iron from the blood stream.

In harmony with the latter hypothesis, in a few previous experiments (10, 16), with intravenous injection of iron, the removal of the iron from the blood stream has been accelerated in patients with hemorrhagic anemia. But this could not be confirmed by the experiments here presented, which were compared with a larger control material than employed in the previous investigations.

### Summary.

1. Examination of 22 patients with hemorrhagic anemia shows in every instance a decrease in the iron content of the serum. In 5 of these patients the lowest values observed were under 20  $\gamma$  %, in 5 between 20 and 39  $\gamma$  %, and in 10 between 40 and 59  $\gamma$  %.
2. After the hemorrhage the iron content of the serum falls rather slowly, so that the lowest values most often are observed from one to several weeks after the beginning of the hemorrhage. In 3 patients a transitory rise in serum iron has been observed shortly after the hemorrhage.
3. Generally the serum iron content keeps at a low level till the regeneration of the blood is completed essentially or even for some time after. This rule is not without exceptions, however.

4. Only a slight correlation is observed between the values for serum iron and hemoglobin, and the variations of the two qualities are not parallel.

5. Ingestion of 1 g of ferrous lactate is followed in 3 out of 5 patients by a greater rise in serum iron than is seen in the control material (15 subjects). In this test the control material shows great individual variations in the height of the iron tolerance curves, but these variations are in no way dependent upon the gastric acidity.

6. Intravenous injection of 10 mg of iron as ferrous lactate shows no definite divergence between 5 patients with hemorrhagic anemia and the control material (10 subjects).

7. The cause of the low values for serum iron in patients with hemorrhagic anemia is discussed.

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From Department II, the Municipal Hospital, Copenhagen, (Chief: Professor H. J. Bing, M. D.; later, H. Heckscher, M. D.) and Dep. A, the General Laboratory of National Health Insurance Physicians (Chief: K. Brøchner-Mortensen, M. D.)

## **Serum Iron in Patients with Hyperchromic Anemia in Idiopathic Steatorrhea.<sup>1</sup>**

By

**KNUD BRØCHNER-MORTENSEN.**

(Submitted for publication December 10, 1942).

A previous paper (2) has given an account of studies on the iron content of the serum in patients with pernicious anemia. In concordance with previous experiences, untreated patients showed increased or high normal values for serum iron, and a pronounced fall in serum iron immediately after the institution of liver therapy.

Only a relatively few studies have been reported so far on serum iron in other hyperchromic forms of anemia.

In patients with hyperchromic aplastic anemia, some investigators (5, 11, 13), obtained values within or above the normal range of variation.

Hotz (9) examined 2 patients with sprue anemia.

One of these patients showed: Hemoglobin 13 %; red blood count 0.54 million. A few days after institution of treatment with liver extracts and two blood transfusions, the patient showed 169  $\gamma$  % serum iron, and under continued liver treatment the value for serum iron fell in about 20 days to 45  $\gamma$  %, and then it kept at a subnormal level.

The other patient showed: Hemoglobin 46 %; red blood count 1.68 millions; serum iron 55  $\gamma$  %.

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<sup>1</sup> The present studies were carried out with the aid of a grant from King Christian X's Foundation.

# Writer's Investigations.

The iron content of the serum was studied in 2 patients with hyperchromic anemia and idiopathic steatorrhea.

As to the analytical technique employed the reader is referred to the description given in previous papers (2, 3, 4).

## Case 1.

Woman, 69 years old. Admitted 22/7—15/8/40 (Reg. No. 8/8/40).

*Diagnosis:* Idiopathic steatorrhea; Hyperchromic anemia.

*History:* During the past year, increasing tiredness; periods with frequent voluminous stools; appetite poor; occasional vomiting. Sometimes paresthesias of the tongue.

*Examination:* Small, thin and pale. Weight 42 kg.

Mucous membrane of the tongue somewhat atrophic.

Abdomen large meteoristic. Temperature normal.

Sedimentation test: 12 mm/1 h. Wassermann negative.

Hemoglobin 65 %. Red blood count 2.19 millions. Color index 1.38. Volume index 1.38. White blood count 5000. White blood picture normal. Platelet count 190,000.

Serum iron 28  $\gamma$  %.

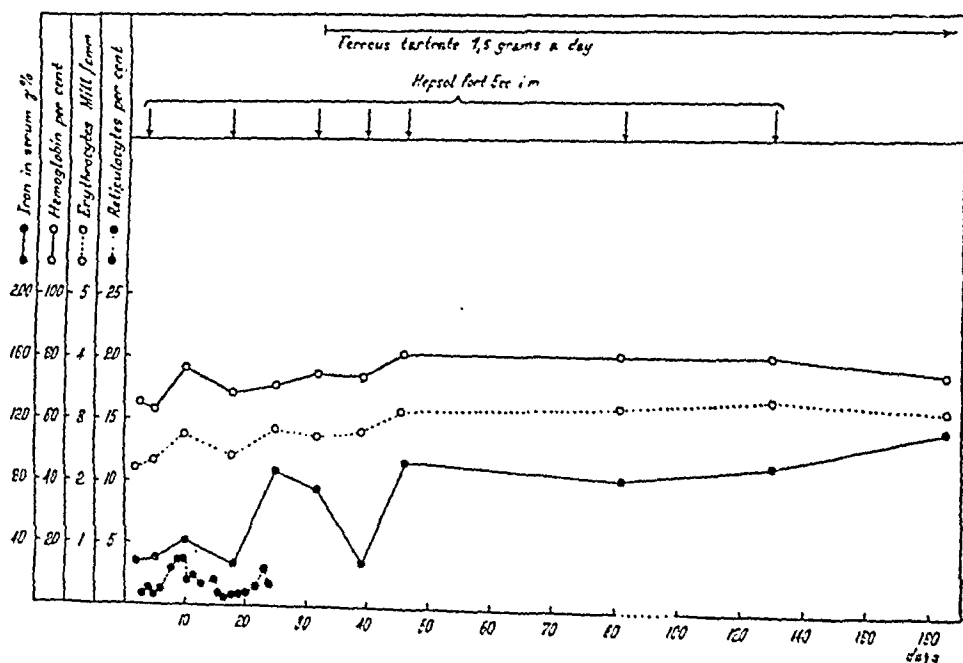


Fig. 1. Iron content of the serum in a patient with hyperchromic anemia and idiopathic steatorrhea. Case 1.

Fasting blood sugar 92 mg %. Glucose tolerance test with 1 g glucose per kg: Rise in blood sugar to 149 mg % in 1 ½ hours, and secondary fall to 67 mg % in 3 ½ hours.

Ewald test meal, I 42 + 31 cm<sup>3</sup>; Free acid 33; Total acid. 53.

» » » II 41 + 30 » » » 42; » » 66.

Feces: No blood. Catalase value 60—110 (Kemp & Thune Andersen's modification of Norgaard's method). Amount: 300—700 g per day. Total fat 30.3 g per day, 9.9 g of this as neutral fats.

Urine: No albumin, pus, blood or sugar.

X-ray exam. of stomach and intestines: No abnormality.

Course: See Fig. 1.

## Case 2.

Woman, 56 years old. Admitted 19/5—16/6/42 (Reg. No. 919/42).

*Diagnosis:* Idiopathic steatorrhea; Hyperchromic anemia; Coliuria.

*History:* For about 2 ½ years, tiredness and paleness, treated with iron to no avail. During the last weeks: Poor appetite, diarrhea, and impairment of muscular power of the legs.

*Examination:* Height 166 cm. Weight 48 kg.

Thin, pale, with dry skin. Mucous membrane of the tongue normal. Moderate impairment of muscular power, especially in the left arm and leg. Patellar reflexes weak. Sensibility normal. Temperature normal.

Sedimentation test: 2 mm/1 h. Wassermann negative. Hemoglobin 69 %. Red blood count 2.90 millions. Color index 1.12 (later rising to 1.5). Volume index 1.37. White blood count 5800. White blood picture normal. Serum iron 28 γ %.

Fasting blood sugar 80 mg %. Glucose tolerance test with 1 g of glucose per kg: Rise in blood sugar to 99 mg % in 3 hours.

Bone marrow, sternal puncture (O. Wanscher): Moderate cellular content in smears. Differential count of 100 white cells shows no definite abnormality; the number of erythroblasts is strikingly low.

|  |    |
|--|----|
| Myelocytes, neutrophils.....                 | 21 |
| » eosinophils + basophils .....              | 3  |
| Metamyelocytes .....                         | 9  |
| Leucocytes, neutrophils, staff-nuclear ..... | 33 |
| » » segment-nuclear .....                    | 19 |
| Erythroblasts, polychromic .....             | 2  |
| » hemoglobin-containing .....                | 6  |
| Reticulum cells .....                        | 1  |
| Monocytes .....                              | 4  |
| Plasma cells.....                            | 2  |
| Lymphocytes .....                            | 10 |

Ewald test meal, I 10 + 16 cm<sup>3</sup>; Free acid 21; Total acid. 40.

» » » II 17 + 18 » » » 7; » » 71.

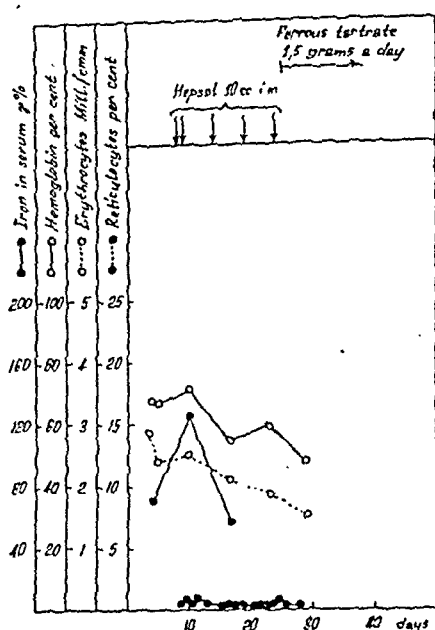


Fig. 2. Iron content of the serum in a patient with hyperchromic anemia and idiopathic steatorrhea. Case 2.

Feces: No blood; somewhat greasy and voluminous. Catalase value 15—60 (Kemp & Thune Andersen's modification of Norgaard's method). Total fat 27.5 g per day, 26.4 g of this as neutral fat. (Daily amount 900 g).

X-ray exam.: Colon normal.

Urine: No albumin, blood or sugar. Microscopy: +++ leucocytes; + growth of colon bacilli.

Basal metabolic rate 98 %.

Spinal fluid: Cells 1 per 3 mm<sup>3</sup>; albumin 5; globulin 0 (Bisgaard). Wassermann negative.

Course: See Fig. 2.

Patient No. 1, a woman, aged 69, who for 1 year had presented symptoms of idiopathic steatorrhea, was now observed for about half a year under treatment with Hepsol fortior MCO (= 100 g of fresh liver per cm<sup>3</sup>) and ferrous tartrate.

On admission, the iron content of the serum was very low (28 γ %), but rose gradually to low normal values. At the same time, the hemoglobin percentage increased from 65 to 81 %, while the blood picture preserved its hyperchromic character.

At the institution of liver therapy, no change was seen in the iron content of the serum. The reticulocyte count rose to 3.5 % in 7 days.

Patient No. 2, a woman, aged 56, who for 2 ½ years had presented symptoms of anemia, and for some weeks symptoms of sprue, was under observation only for a relatively short time.

On admission the iron content of the serum was slightly subnormal (70  $\gamma$  %). Under treatment with Hepsol MCO (= 5 g of fresh liver per cm<sup>3</sup>) the serum iron rose to 127  $\gamma$  % in 2 days and then it fell off again to 59  $\gamma$  % in 9 days.

The hemoglobin percentage showed a fairly gradual fall from 69 to 49 % while the hyperchromic character of the anemia was accentuated. No rise in the reticulocyte count was observed under the liver treatment.

After intravenous injection of 10 mg of iron as ferrous lactate the iron content of the serum was seen to increase from 70 to 236  $\gamma$  %, and this was followed by an excessively rapid fall to 118  $\gamma$  % in 1 hour (a fall of 118  $\gamma$  %) and 92  $\gamma$  % in 2 hours (a fall of 144  $\gamma$  %).

As mentioned in a previous paper (2), a control material, comprising 10 subjects, whose iron metabolism had to be considered normal, responded to the same treatment with a fall in serum iron of 30—108  $\gamma$  % (averaging 60  $\gamma$  %) in 1 hour, and 52—106  $\gamma$  % (averaging 83  $\gamma$  %) in 2 hours.

### Discussion.

Of two patients with untreated hyperchromic sprue anemia one showed a marked decrease in serum iron, the other a moderate decrease. No additional fall in serum iron was seen after treatment with liver extract.

The examination of these patients thus showed a considerable deviation from the findings in patients with pernicious anemia.

As mentioned above, previously only one author (9) has looked into the serum iron in patients with sprue anemia. One patient was found to show a decrease in serum iron corresponding to the one here observed. The other patient, who had received two blood transfusions the preceding days, showed normal values, and later subnormal values.

Our knowledge concerning the pathogenesis of hyperchromic sprue anemia is very incomplete (6, 7, 8, 10, 12, 14).

On examination of a large number of patients with tropical sprue, Castle, Rhoads, Lawson & Payne (6) found that administration of «extrinsic factor» alone had a favorable effect on some patients, while in other patients such an effect was obtained only on simultaneous administration of stomach contents from normal persons. In some cases the ingestion of liver extracts was relatively inactive, whereas they proved active when given parenterally. In the liver of one patient who died of sprue no trace of the «antipernicious principle» could be demonstrated. The authors thought it justified, therefore, to conclude that hyperchromic anemia in some cases is due to deficiency in «extrinsic factor», in others to deficiency in «intrinsic factor», and, in particular, that the absorption of the «antipernicious principle» was lowered in several cases.

The cause of the decrease in serum iron in patients with idiopathic steatorrhea cannot be ascertained on the basis of these findings.

Generally the iron content of the serum is dependent on a number of more or less established factors: the absorption of iron from the digestive canal, the storage of iron and its mobilization from the depots, the consumption of iron in the formation of hemoglobin, the liberation of iron under decomposition of hemoglobin, and the somewhat obscure metabolism of iron by the cellular parenchyma.

As pointed out more explicitly in a previous paper (1), for the present we have to reckon that measurable amounts of iron are practically never excreted from the organism, and that iron is absorbed only under particular circumstances: during growth and pregnancy, after loss of iron through hemorrhage, and after intake of rather large amounts of soluble iron salts.

Accordingly, the decrease in serum iron observed in these patients cannot be due to a decreased absorption of iron that has to be attributed to changes in the intermediate iron metabolism. The experiment with intravenous injection of iron performed on one of these patients showed an unusually rapid migration of the iron out of the blood stream. At present, however, it is hardly possible to form any well-founded idea as to whether this iron has been taken up by the depots, the bone marrow or other tissues.

Patients with infectious diseases or cancer show usually a considerable decrease in serum iron even in the absence of anemia. The cause of this decrease is not established with certainty.

The patients studied here presented no sign of cancer, and as to infectious lesions, only one of them showed merely the presence of non-febrile coliuria, which could hardly have caused any decrease in serum iron.

The previously prevailing view that sprue might be of infectious origin appears not to be justified after the various findings reported so far (8, 10, 14).

### Summary.

1. Two patients with untreated hyperchromic anemia and idiopathic steatorrhea show respectively 28 and 70  $\gamma$  % serum iron. No additional decrease in serum iron is seen after treatment with liver extract.

2. In one of these patients, intravenous injection of 10 mg of iron as ferrous lactate is followed by an unusually rapid migration of the iron out of the blood stream.

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## Revue des Livres.

Fr. Agostino Gemelli O. F. M.: *La Psicologia a servizio dell' orientamento professionale nelle scuole* (Zanichelli, Bologna 1943, 250 p.).

L'auteur de cet ouvrage est président de la commission permanente pour les applications de la psychologie du conseil national des recherches scientifiques. Le volume contient les chapitres suivants: prémisses, notions fondamentales, conceptions erronées, les voies de la réalisation de l'orientation professionnelle, le problème médical, la tâche du psychologue, la tâche de l'éducateur, opinions diverses sur la nature des aptitudes, la position du problème des aptitudes, l'analyse des facteurs, tendances, inclinations et intérêts comme prémisses du jugement qui est à la base de l'orientation professionnelle, diagnostic des tendances et des inclinations, méthodes de l'école pour le jugement de l'élève concernant l'orientation professionnelle, continuation de l'orientation professionnelle, conclusions.

Les conclusions de l'auteur peuvent être résumées comme suit:

L'orientation professionnelle est un problème scientifique. Elle repose sur les thèses suivantes: a) Il existe plusieurs différences psychiques et psychophysiques entre les hommes; b) notre activité psychique oscille entre une stabilité relative et une variabilité relative, elle possède une plasticité relative, surtout pendant la période évolutive de la vie, avec les progrès de l'âge, la stabilité s'accroît, de sorte qu'à la fin de la période évolutive la personnalité de l'être normal a pris une physionomie propre; c) l'activité psychique obéit à des lois, de sorte que les manifestations psychiques présentent une constance suffisante, qui permet de les classer en



catégories, de saisir des connexes de successions et d'en prévoir les manifestations.

II. Pour être à la hauteur de sa tâche, l'éducateur doit avoir une connaissance adéquate de la psychologie.

IV. L'orientation professionnelle doit être continue, se poursuivre pendant toute la période scolaire et ensuite pendant toute la vie, car l'homme peut subir une réduction de sa capacité par suite de quelque maladie et, même sans l'intervention de ce facteur, l'activité humaine se modifie continuellement sous l'influence des changements sociaux.

V. L'auteur prend position tout ensemble contre ceux qui ne croient ni à la psychotechnique ni à la psychologie et contre les fanatiques de la psychotechnique.

Ayant déblayé le terrain des conceptions erronées sur la psychologie et la psychotechnique, l'auteur arrive aux conclusions positives suivantes.

1. Dans le choix de la profession, il faut tenir compte des aptitudes, lesquelles sont diverses et nombreuses, quelques-unes spécifiques à certaines professions, d'autres communes à plusieurs professions. Mais il faut tenir compte surtout de la totalité des aptitudes, ce qui revient à dire que l'orientation professionnelle se base sur une évaluation globale des aptitudes du sujet.

2. Toutefois, le jugement qui dirige l'orientation professionnelle doit donner plus d'importance à la constatation des inclinations, des intérêts et des tendances de l'individu qu'à l'évaluation globale des aptitudes, afin de pouvoir déterminer le noeud central de sa personnalité, surtout les éléments émotifs du caractère et du tempérament, qui sont le ressort de l'activité humaine.

3. L'orientation professionnelle se base sur le diagnostic de la personnalité qui résulte de l'évaluation globale des aptitudes, des intérêts, des inclinations et des besoins de l'individu et de la détermination des possibilités existantes d'employer utilement le sujet qui possède ces aptitudes et traits caractérogiques pour une tâche déterminée dans les conditions sociales où elle doit être remplie. D'où il suit que l'orientation professionnelle qui a lieu à l'école n'est pas quelque chose d'absolu qui s'impose au sujet, comme la conçoivent quelques nations. Elle doit être plutôt une indication utile, un conseil paternel et amical donné à l'élève qui se prépare à l'école à exécuter pendant sa vie une fonction utile à

lui-même et à la société. Il faut donc que l'orientation professionnelle soit une assistance humanitaire donnée à l'individu.

4. L'orientation professionnelle ne se résume pas dans une technique d'orientation. Elle a une tâche plus vaste que la détermination de la capacité, des aptitudes et des inclinations d'un individu. Dans un sens plus large, elle est une fonction de l'école, car l'orientation et l'éducation sont deux aspects de la même fonction éducatrice, qui tend à préparer l'enfant, l'adolescent et le jeune homme à devenir un citoyen d'une patrie terrestre.

5. L'orientation professionnelle exige une observation patiente et continue pour suivre l'évolution de l'individu sous l'influence de l'éducation. Les aspirations de l'adolescent sont le plus souvent en conflit avec les exigences de la vie et avec le patrimoine psychique, intellectuel et moral de l'adolescent. Il appartient à l'éducateur de résoudre ce conflit en ramenant l'adolescent sur le terrain d'une réalité illuminée par de nobles idéals. Les rêves de l'adolescent doivent céder la place aux aspirations concrètes et positives que l'éducateur doit cultiver et fortifier. Cette orientation doit être continuée longtemps afin de permettre à l'éducateur de corriger les erreurs éventuelles de son jugement sur l'adolescent, ce qui est d'autant plus important que l'adaptation sociale se prolonge après la fin de la période scolaire.

6. L'orientation a une action éducatrice en ce sens qu'elle doit envisager la conciliation des idéals de la vie et des exigences de la vie elle-même, en transformant les aptitudes, tendances et intérêts innés en aptitudes, tendances et intérêts professionnels.

7. L'activité de l'orientation professionnelle doit être le résultat d'une coopération entre: a) l'éducateur, qui doit préparer l'individu à la vie et le stimuler à choisir lui-même sa propre voie; b) le *médecin* qui doit signaler les traits constituant des contre-indications de certaines professions; c) le *psychologue*, qui donnera à l'éducateur les moyens de substituer aux jugements intuitifs, de valeur discutable, des méthodes positives; d) la *famille*, qui est directement intéressée au choix professionnel de l'enfant; e) les *organisations professionnelles*, qui doivent préparer des hommes utiles à la nation.

8. Pour l'homme de notre époque, la profession est devenue un élément important de la vie. Bien qu'on prétende que l'homme a le droit de choisir sa profession, ce droit est restreint par les

conditions mésologiques et économiques, par les exigences sociales, par une série infinie de facteurs qui font de la profession une prison, dont l'individu tente en vain de s'évader. Certains excès et abus typiques des divertissements propres à notre époque, tels que le cinéma et les sports, ne sont que des manifestations de ces tentatives d'évasion. Si l'individu ne peut pas se soustraire à une profession pour lui désagréable, il en résulte une série de conflits plus ou moins douloureux: avec la famille, avec les camarades de profession, avec soi-même. Dans la genèse des névroses un certain nombre de facteurs proviennent d'influences professionnelles constituant des causes de conflits, facteurs dont les plus décisifs sont ceux qui tiennent à la distance entre ce qu'aurait voulu être l'individu et ce qu'il est en réalité, au contraste, par exemple, entre la pauvreté réelle et la richesse souhaitée, entre la position modeste dans la profession et l'aspiration à une position dirigeante, entre un travail monotone et ennuyeux et un métier personnel et plein de variété. Ainsi la profession devient au cours des années, pour nombre d'individus, une camisole de force qui absorbe toute leur activité sans leur laisser aucun moyen de vivre selon leur propre goût.

L'idéal serait évidemment de faire concorder les aptitudes, inclinations et intérêts individuels avec une profession donnant les satisfactions matérielles, psychologiques et morales désirées. Mais dans la société actuelle on n'y arrive presque jamais, sauf dans l'état de paysan, au sujet duquel Spranger rappelle le mot de J.-J. Rousseau: «le paysan est le seul homme véritable.»

L'orientation professionnelle est le moyen auquel recourt la société moderne pour rendre moins durs et moins graves les funestes effets de cette situation. Elle est aussi le moyen de rendre moins fréquents les cas où un homme est contraint d'exercer un métier qu'il n'aime pas, qui ne correspond pas à ses goûts, à ses tendances et à ses intérêts. Elle mettra au moins les hommes en état de choisir, dans la mesure des possibilités réelles de la vie, une profession moins éloignée de l'idéal que chacun se fait d'un métier et partant plus supportable.

Le livre de M. Gemelli mérite d'être étudié par tout homme qui s'intéresse à la question de l'orientation professionnelle, dont l'importance grandit de jour en jour dans la société moderne.

Olof Kinberg.

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19 & 20, 1942,*

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From the Medical Department's Ambulatorium, Finsen Institute,  
Copenhagen. (Physician in Chief: A. Hecht Johansen, M. D.).

## On Calcinosis.

Calcinosis universalis in a man with uric-acid diathesis and hypogonadism, and typical Calcinosis circumscripta in a woman.<sup>1</sup>

By

JØRGEN PEDERSEN.

(Submitted for publication December 1, 1942.)

Interstitial calcinosis is a rather enigmatic disease, manifested by multiple calcareous deposits in mesenchymal tissue, especially in subcutis. As yet the aetiology and pathogenesis are unknown; in particular, no definite or constant changes have been observed in the calcium and phosphor metabolism. No effective therapy is known, despite the publication of certain remarkable therapeutic results.

Comprehensive surveys of the subject have been given by various authors. In 1938 Atkinson & Parkes Weber (2) collected 215 cases of the disease from the literature (137 of calcinosis circumscripta and 78 of calcinosis universalis). Reference may also be made to Steinitz's large work (35), to Brooks (7) and Durham (12, 13), as well as to Weissenbach et al. (44, 45, 46, 47, 48) who deal especially with calcinosis in its frequent combination with scleroderma, which many call by the name of »syndrome de Thibierge-Weissenbach». In Scandinavia too the disease has attracted

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<sup>1</sup> Read before »Dansk Selskab for Intern Medicin» on Dec. 11th 1942. Demonstration of radiograms before »Dansk Radiologisk Selskab» on Nov. 18th 1942.

much attention; there are about twenty reports of such cases in this part of the world.

No complete disquisition on the subject need be given here, as it is fully dealt with in the publications quoted above. Some points will be touched upon in the Discussion.

The following facts may be given for purposes of orientation:

According to Steinitz (35) a distinction is made between two clinical pictures: circumscribed calcinosis and universal calcinosis; first and foremost they represent a difference in occurrence, but as a rule their course is different too, especially with regard to prognosis. Delimitation between the two forms is not sharp. Whether or not an original circumscribed form can develop into the universal form is an undecided question, and especially we do not know if there is a difference in aetiology and pathogenesis between the two pictures.

*Circumscribed calcinosis:* the deposits are not much diffused and in most cases occur in the form of pea-sized calculi in subcutis and cutis around the small joints of the extremities, especially in finger pulvae. The disease affects women especially, in and after the menopause; it causes only local inconvenience. The fingers become tender to pressure and joint movement may be restricted. Sometimes calcium is excreted after redness and inflammation in the skin, whereafter it is usual for new deposits to form. Patients often have scleroderma or Morbus Raynaud, or suffer from more or less pronounced acrocyanosis. This also applies to the universal form. Prognosis is good quoad vitam.

The following case record may serve as an example:

Sent by the Finsen Institute's surgical department (J. 11515). A 62-year old unmarried masseuse, observed since 1936. Previously well on the whole. Menses normal, menopause 48 years old. Nine years ago (1933) a hard, tender nodosity appeared on the pulpa of the right index finger some time after she had pricked herself there with a needle. Similar nodules appeared on other fingers during the next few years. The tenderness was so great that she had to give up her work as a masseuse, and in 1936 she was granted an invalidity pension. Besides the extreme tenderness there were at intervals redness and swelling and abscesses at the site of the hard nodules. On three occasions incisions were made. Three years ago (1939) a pea-sized, red tender nodule appeared on the back of the right elbow. During the last few years she has suffered from blue and cold hands; there have been no paroxysmic attacks of pain.

For some years the patient has complained often of tiredness and depression. Otherwise there are no organic symptoms.

Physical examination (1942) shows a somewhat senile and depressed woman.

Upper extremities: The skin of the hands is smooth and somewhat atrophic, soft, easily folded. The colour is slightly bluish (very blue at the time of several previous examinations). On the right hand, on the volar side of each of the three radial fingers, one can feel two subcutaneous, barely pea-sized hard nodules adhering to the skin. On the left hand there is one nodule on each of the three radial fingers and one in the right vola manus. Some centimetres distally to the right olecranon is a pea-sized, red nodule on the radial side; it is hard and hot to the touch. (Fresh calcium exudations). All the joints of the extremity are free.

Lower extremities: Skin and joints natural. Under the transversal arch in the planta of the right foot are three keratoses, somewhat tender, about the size of a threepenny piece.

Remaining examination reveals nothing abnormal.

Blood pressure, haemoglobin, sedimentation rate, urine, serum calcium, serum phosphor, serum phosphatase: all normal at repeated examinations during the years. Blood uric acid a.m. Brochner-Mortensen (9), in all four tests after ordinary diet in the period 12. 10. 41 to 24. 6. 42: 7.8, 10.1, 7.2, 7.8 mg% (normal < 8.5 mg%).

Chemical analysis of calcium grains shows that they consist of calcium phosphate and carbonate. No uric acid.

Histological examination of tissue: amorphous concretions of calcium in subcutaneous connective tissue without inflammatory reaction.

Radiograms through the years show an increasing number of calcareous deposits in the subcutaneous tissue of the hands. The deposits vary in size from millet to pea. In 1941 small calcium concretions visible for the first time in the subcutaneous tissue of the forearm. Radiograms of upper arms and lower extremities show nothing abnormal.

*Epicrisis:* After the menopause a depressive woman with a disposition for blue and cold hands has a slowly increasing number of subcutaneous calcium concretions on both hands and forearms. The nodules are so tender that she has to abandon her work as a masseuse and she is awarded invalidity pension.

In addition to the nodules the skin of the hands is atrophic and rather cyanotic. The joints are quite free. Examination reveals nothing abnormal otherwise; in particular the blood-chemical tests are normal. (Regarding blood uric acid, see Discussion.)

This is a typical case of calcinosis circumscripta, the form which the French call «concrétions calcaires des atrophies cutanées».

*Universal calcinosis:* In this type the calcium deposits are very numerous, especially around the large and small joints; in particular there are numerous small deposits, »fluff». Apart from cutis and subcutis, the calcium is also deposited in the muscular interstices, in connective tissue around nerves, in fascies and sinews. The calcium is almost always situated in the extremities, more rarely in the trunk and in the head. The disease is rare, occurring almost with equal frequency among both sexes. It is observed especially among relatively young people, and even in children. The disease is chronic and progressive and, besides causing local inconvenience, may affect the general condition. A patient may become more or less stiff and helpless, and some die of infection and muscular changes. Thus very often it is a very grave disease.

Below is a report of a case of *universal calcinosis* in curious combination with other diseases.

#### *Case report.*

A 48 year old man, married mechanic, sent to the medical ambulatory in September 1941 for treatment for arthritis urica (J. 9537).

*Anamnesis:* Has not had scarlatina or diphtheria.

In 1903 — when 10 years old — a piece of bone was removed from under the right heel, which had become about 2 ½ cm higher than the left heel.

In 1911 — 18 years old — acute rheumatism. He had pyrexia and shifting joint swellings. Was treated at home by his doctor; thinks he had no cardiac complication. As a result of the rheumatism he was rejected for military service.

Since 1923, at the age of 30, he has periodically had pains in the joints, including three well-marked attacks of gout; in addition, pains, swelling and redness of the left wrist, right elbow, and both ankles. Only slight attacks in the fingers and never any swelling of shoulders or knees. Has felt feverish during the joint attacks. In the period from 1936 to 1939 has been treated with inter alia 24 »Atophan» tablets (cinchophen) with good effect.

In the autumn of 1939 he twice had joint attacks, for which he was treated in the medical department of Frederiksberg Hospital.

From the case-book of the department (319/40)<sup>1</sup> we read:

1. Hospitalized 25. 8.—23. 9. 39. Diagnosis: Arthritis urica. Ill four days prior to hospitalization with pain, swelling, redness of left wrist and pain in right metacarpo-phalang. joint I. Taken »Atophan» tablets at home with some effect.

<sup>1</sup> I thank N. R. Christoffersen, M. D. physician-in-chief at the Frederiksberg Hospital, for kind permission to make use of the record.



Physical examination revealed left wrist swollen, red and tender. Movement slightly restricted. The left elbow, which otherwise seems natural, lacks 40—45° of full extension. The other joints natural.

On the anterior side of the right femur and on the left crus is a loose, longish infiltration. No tophi, and on the whole no other abnormality. Temperature was sub-febrile during the first eighteen days in hospital, the maximum being 38.2 on the second day.

Sedimentation rate 31 mm. — 2 mm in an hour. Gonorrhoea test:  $\div$ . Urine test: normal. uric acid in blood a.m. Folin & Benedict (normal < 4 mg %): 20. 8. 39, 5.3 mg %, 2. 9. 42 7.4 mg %.

Up to 1. 9. 39 he had slight pains in various joints, but nothing abnormal could be found. After that he felt well. Treatment: bed, colchichin, cinchophen, mud pack.

2. Hospitalization 8. 12. 39.—29. 2. 40. Diagnosis: Arthritis urica.

During the month prior to admission the patient lay in bed at home on account of «attacks» in the left foot, ankle and calf. There was also tenderness in both shoulders and both sides of the loins. The left wrist was normal.

Physical examination: Slight tenderness to pressure on the shoulder and articulatio metacarpophal. joint I sin. On the anterior side of the right femur, localized to m. quadriceps femoris, rather severe tenderness. Left crus slightly thickened and very hot compared with the right crus. Left crus a little tender to pressure. Left foot much swollen and hot. Motility of artic. talo-cruralis and talo-calcaneus greatly restricted. Other joints natural.

Temperature sub-febrile the first 68 days in hospital, maximum 38.3. Sedimentation rate 16 mm — 4 mm one hour.

Wassermann and gono-reactions: —. Urine normal.

Blood uric acid 9. 12. 39 5.6 mg %, and 30. 12. 39 6.1 mg %.

A day or two after hospitalization there came swelling, pain and restricted motility of the right foot.

On two occasions an attack of «arthritis urica» in the metatarso-phal. joint of the right great toe.

As on the previous hospitalization there was trouble in various joints, especially in the left elbow and wrist, with some pain. The swelling of the foot joints and of left crus varied a good deal, but had practically subsided on discharge. Treatment as on first occasion.

During the past two years this patient's condition has been perfectly good in periods, but he had joint attacks now and then as before. On the back of the right elbow a red, tender nodule has appeared and emitted pus at intervals. At times there has been «blood poisoning» of the right upper arm from the fistula. The attacks subside to hot fomentations.

Came to the Finsen Institute, mostly for pains in the right elbow. Examination here gave the following:

The patient's appearance natural, perhaps somewhat younger than his age. Is quiet, not neurasthenic.

Skull, eyes, tongue, fauces: normal.



Fig. 1. Calcifications in the subcutaneous tissue of the left foot. «Fluff».

Teeth: fairly good, one or two molars decayed.

Heart, lungs, abdomen: natural. Blood pressure 145/80.

Extremities: The skin somewhat dry, not atrophic or sclerodermic, colour natural. No skin disease of any kind.

Joints: The outer joint of the left fifth finger thickened. Motility slightly restricted. Both wrists slightly thickened with some tenderness to pressure. Volar flexion natural, dorsal flexion only about 10°.

Left elbow of normal appearance. Somewhat tender to pressure. Motility from 65 to 170°.

Right elbow natural except for slight swelling and skin redness at the site of bursa olecrani.

Other joints normal.

No tophi on the ears, but closer examination revealed some hard nodules of varying size, mostly from grain to hazel-nut size, in subcutis and cutis on the radial side of the right wrist, on the radio-dorsal side of the left wrist, on the front of the right femur (size 4 × 6 cm), back of the right knee, right achilles tendon, front of the left talo-crural joint and left dorsum pedis.

Other examinations:

*X-ray:*

Radiograms were made of the whole body.

Those of the extremities showed: Deposits of calcium in the subcutaneous tissue on all the pictures. It is well marked on the fingers and around the wrists and elbows; on the volar side of the left elbow is a nut-



Fig. 2. Large calcium deposits around the left knee.

sized calcification on the site of fossa coronoideum ulnae; on antebrachia there are fewer, finer deposits. In the soft parts over the right clavicle are two pea-sized calcifications. Around the ankles the subcutaneous and interstitial tissue is quite-marbled with calcium, on the feet the concretions are as fine as fluff (fig. 1). Under left tuber calcanei is a calcium concretion  $3 \times 1.5$  cm in size.

Calcifications are also visible on crura; around the knee joints considerable quantities; in the back of the right knee several nut-sized calcifications (fig. 2).

On the medial side of femora is an irregular, longish calcification with a suggestion of osseous structure; it is about 15 cm long and apparently lies in one of the muscle interstices (fig. 3).

On the pictures of the pelvis there are two phlebolites. On the right crista iliaca is an irregular bone formation, 5 cm wide and  $2 \frac{1}{2}$  cm high, in structure and appearance resembling an osteophyte.

On the side of columna, 5 cm to the left of the 3rd and 4th lumbar vertebrae are two calcifications, one pea-size, slightly marbled, the other nut-size. They are both outside the kidney shadow.

I. v. urograph: natural.

Radiograms of lungs, heart and skull: natural.

Sella turcica: somewhat small, of natural shape. Dimensions  $8 \times 5$  mm.

All bones are normal in appearance, as also all joints except for minimal



Fig. 3. Calcifications with a suggestion of bone structure, from the right femur.

changes like arthrosis deformans in the wrists. Nothing in the pictures to suggest arthritis urica. No gall stones to be seen.

Roentgen diagnosis: Calcificatio interstitialis universalis. (signed Worning).

Sample borings were made 21. 10. 42 at the Radium Station through skin and calcareous deposits on the right femur. The tissue gave no murexide reaction.

#### Histological examination:

Epidermis seems somewhat flattened, corium poor in nuclei, continuing into the subcutaneous connective tissue and fatty tissue in which are groups of sweat glands. In the subcutaneous connective tissue are deposits of large, irregularly shaped, sometimes rather spongy flakes of amorphous substance which stains blue with haematoxylin like calcium. Delimitation against the connective tissue is quite sharp, and apparently the tissue does not react to the calcium deposits: in particular there are neither round-cell infiltrates nor intrusive giant cells (fig. 4).

In Gieson-stained sections the connective tissue in places is poorly stained and poor in nuclei indicating local degenerative changes. At several places in the calcium deposits there is a distinct organization of the tissue; there are tissue formations recalling bone spongiosa, there being diffuse cell nuclei inside the calcium substance surrounded by a clear cavity (fig. 5), at the same time, on the border to the connective tissue the latter is denser in places, especially in the form of augmented cell nuclei, like the development of a periosteum. There is no doubt that the picture is one of actual ossification of the connective tissue.

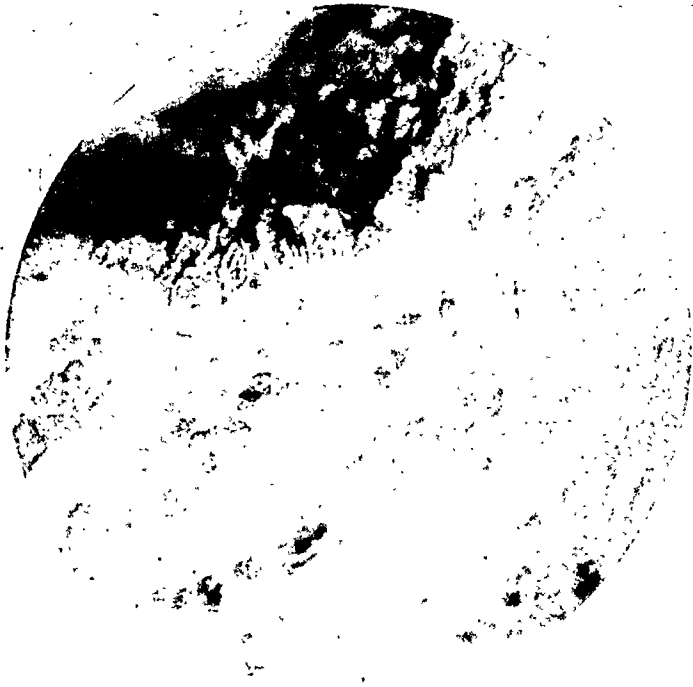


Fig. 4. Amorphous calcium deposits in subcutis on the right femur. No reaction in the surrounding connective tissue.  
Stain: haematoxylin-eosin.  $\times$  circa 300.

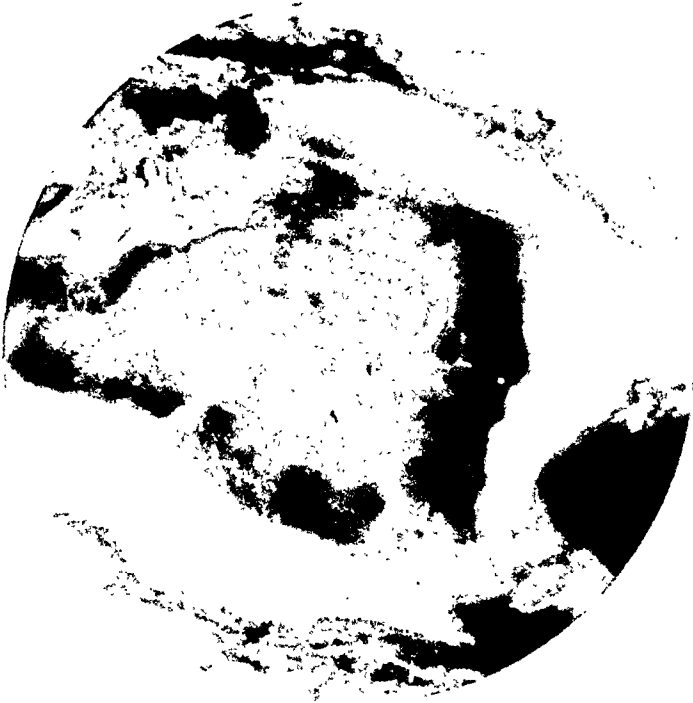


Fig. 5. Incipient bone formation in subcutis on right femur. Cell nuclei surrounded by clear cavities lying diffusely in the calcium substance.  
Stain: van Gieson-Hansen.  $\times$  ca. 300.

Table 1.

Cases of calcinosis with increased blood uric acid.

| Author                                | Sex | Age | Uric Acid <sup>1</sup> |                         |         | Remarks                           |
|---------------------------------------|-----|-----|------------------------|-------------------------|---------|-----------------------------------|
|                                       |     |     | Highest value mg %     | No. of deter- minations |         |                                   |
|                                       |     |     |                        | of in- creased values   | in all  |                                   |
| Calcinosis circumscripta              |     |     |                        |                         |         |                                   |
| 1. Weil & Weismann- Netter (43) ..... | ♀   | 52  | 67.8                   | Several                 | Several | Adenoma thyreotoxic.              |
| 2. do. ....                           | ♀   | 47  | 8.5                    | Several                 | Several |                                   |
| 3. Garcin & al. (14) ....             | ♀   | 65  | 5.4                    | 1                       | 1       |                                   |
| 4. Weissenbach & al. (16)             | ♀   | 56  | 4.8                    | 1                       | 1       | Insuff. cordis exophthalmus       |
| 5. Houcke & Warem- bourg (24) .....   | ♀   | 80  | 5.4                    | 1                       | 1       |                                   |
| 6. Strauss (36) .....                 | ♀   | 60  | ca. 5                  | 1                       | 1       |                                   |
| 7. Wilson (51) .....                  | ♀   | 57  | 4.4                    | 1                       | Several | Diagnosis of calcinosis uncertain |
| 8. Pedersen, J. ....                  | ♀   | 62  | 10.1                   | 1                       | 4       |                                   |
| 9. Krauss (27) .....                  | ♂   | 73  | 11                     | 1                       | 1       |                                   |
| Calcinosis universalis                |     |     |                        |                         |         |                                   |
| 10. Pedersen, J. ....                 | ♂   | 48  | 11                     | 7                       | 8       |                                   |

<sup>1</sup> For Nos. 1—5 the values given are for «acide urique plasmat». Normal value 3.5—4.5—5 mg %.

For Nos. 6, 7 and 9 the method was Folin's, or a variant of it. Normal value < 4—4.5 mg %.

For No. 8 the Brochner-Mortensen method was employed. Normal values: ♀ < 8.5 mg %, ♂ < 9.5 mg % on ordinary diet. Both the latter and Folin's methods were used in Case 10.

Diagnosis: Degenerative changes in the subcutaneous connective tissue with calcification and ossification. (signed: F. Bang).

Subsequently a flat piece of calcium, 40×60×4 mm., was removed from subcutis on the right femur; it was intimately connected with the muscle fascia. A smaller piece, 5×10×3 mm., was also removed from subcutis on the anterior surface of the left crus.

Powder diagram a.m. Debye-Scherrer (10) revealed both calcium shadows to consist of colloidal apatite. Chemical analysis shows that the samples contain albumen, but neither uric acid nor cholesterol. (This analysis was kindly made by A. Tovborg Jensen, B. Sc., and J. E. Thygesen, M. D. who will make a report in an appendix to this work).

Table 2.

Cases of calcinosis with high cholesterin values.

| Author                                   | Sex | Age | Cholesterol<br>mg % | Metabolism | Remarks                 | Cholesterol in<br>Concretions |
|--|-----|-----|---------------------|------------|-------------------------|-------------------------------|
| <i>Calcinosis circumscripta</i>          |     |     |                     |            |                         |                               |
| 1. Wilson (51) .....                     | ♀   | 57  | 480                 | normal     |                         | ÷                             |
| 2. Weissenbach and al.(47)               | ♀   | 55  | 290                 | "          |                         | (+)                           |
| 3. Ducasse (11) .....                    | ♀   | 50  | 270                 |            | Access of<br>Gallstones | +                             |
| 4. Weil & Weismann-<br>Netter (43) ..... | ♀   | 52  | 250                 | 115        |                         | ÷                             |
| 5. do. ....                              | ♀   | 47  | 250                 | 119        |                         |                               |
| 6. Weissenbach and al.(48)               | ♀   | 41  | 234                 | 120        |                         | (+)                           |
| 7. Steinitz (35) .....                   | ♀   | 82  | 230                 |            | Access of<br>Gallstones | ÷                             |
| <i>Calcinosis universalis</i>            |     |     |                     |            |                         |                               |
| 8. Grenaud & Lescoeur(15)                | ♀   | 9   | 230                 |            |                         | ÷                             |
| 9. Pedersen, J. ....                     | ♂   | 48  | 277                 | 107        | Hypogonadism            | ÷                             |

The following results were also found:

Weight 70 kg, height 164 cm. Urine normal, both microscopically and chemically.

Wassermann and Gono-reactions: —. Haemoglobin % 105. Leucocytes 7000. Erythrocytes 5.1 million. Index colour 0.96. Differential count of white corpuscles normal. No basophil red corpuscles. Sedimentation rate 7 mm/1 hr.

Icterus index, blood urea, serum chloride and bicarbonate, ascorbic acid, antistreptolysin titer, normal. Standard metabolism and glucose tolerance test, normal.

Serum calcium: 10.4 mg%. Serum phosphor 3.04 mg%. Serum phosphatase 43 units (normal).

Blood uric acid a.m. Brochner-Mortensen (9), in all four tests after ordinary diet in the period 12. 9. 41 to 27. 1. 42: 9.1, 10.3, 10.6, 11 mg % (normally < 9.5 mg%).

Serum cholesterin 3. 12. 41 275 mg%, 29. 1. 42 279 mg% (Görlz (18)).

Hormone analyses<sup>1</sup> of 24-hour urine 4. 12. 41 and 29. 1. 42.

Gonadotropin: > 50 mouse units and circa 50 mouse units respectively (normally < 50 m.u.).

<sup>1</sup> The analyses were made by the State Serum Institute's hormone department (Chief: Dr. Chr. Hamburger) making use of the department's usual methods [see e. g. Hamburger & Godtfredsen (20)].

Oestrogen:  $> 20 < 50$  mouse units at both analyses (normal).

Androgen: 14 I.U. androsteron at both analyses (normally  $> 20$  I.U.).

Preliminarily the patient has been treated with short-wave diathermy locally on the right elbow and both feet, without noteworthy improvement.

Treatment had to be discontinued for a time on account of lymphangitis in the right upper arm from the calcium fistula on the elbow. The lymphangitis subsided to hot fomentations with the patient in bed.

Regarding his family the patient states that no other case of calcinosis is known, but his mother is an invalid from rheumatism.

The lady kindly consented to an examination at home and to the taking of a blood sample. She is 74 years old. Three normal partus. Menopause twenty years ago. Pleurisy twice in her younger years, otherwise well. For the first time about twenty years ago had pains in ankle, knees and thumbs. Often had pains since then, but never redness or acute swellings of the joints, nor has she ever had an attack of gout. Does not think she has had pyrexia. In the course of time, the last thirteen ears especially, the hands, knees and feet have slowly and steadily become swollen and deformed. She has been an invalid these last four years, being practically unable to walk on account of her knees; she is unable to dress herself.

Has been treated with acetylsalicylic acid, but never «atophan».

Physical examination: a mentally well-preserved, adipose, invalid woman. Her joints give the picture of a typical progressive primary chronic polyarthritis with marked deforming and subluxation of the fingers, which deviate ulnarly. Marked atrophy of the hand muscles.

The knees are much thickened, deformed, with little motility and audible grating. Elbows and ankles less affected. Other joints seem natural. No tophi of any kind perceptible by palpation.

Urine normal. Sedimentation rate 30 mm/1 hr. Haemoglobin % 78. Erythrocytes 4.49 millions, leucocytes 7,800. Differential count natural. Blood uric acid normal 3.8 mg% (Folin & Benedict).

X-ray photography could not be performed.

Commentary: There is nothing to suggest a diagnosis of calcinosis or arthritis urica, though these diagnoses cannot definitively be ruled out after the examinations made.

*Epicrisis:* A 48 year old man. When a boy had a piece of calcium concretion removed from one heel. During the past thirty years has suffered from many attacks reminiscent of uric acid gout in various joints, most frequently in the great toe, ankles and wrists. Treated twice in hospital and several times at home for arthritis urica.

Examination revealed a universal calcinosis with particular localisation periarticularly. There was also constantly increased



blood uric acid. The joints present no sign of arthritis urica, and there is no uric acid in the concretions.

Next, there are high blood cholesterin, increased gonadotropin and reduced androgen excretion in the urine.

### Discussion.

We have made the following diagnoses on this patient: Calcinosis universalis, arthritis urica or uric acid diathesis and hypogonadism.

The diagnosis of calcinosis is an obvious one. As mentioned, there was no skin diseases. The concretions began at the latest in boyhood, and the disease has been rather benignant despite its wide diffusion; his ability to work is somewhat reduced, however, mainly owing to pains.

The diagnosis of arthritis urica is based on the increased blood uric acid. A total of eight tests in the course of 30 months with various methods the blood uric acid was found to be greatly increased on seven occasions.

The patient's joints are very little affected, clinically, beyond what is due to the calcinosis, and roentgenologically there is no sign of arthritis urica; as such finds can be made even after several years of arthritis urica, this does not argue against the diagnosis. Furthermore, we may preclude other well-known causes of the increased blood uric acid, e. g. infectious disease, blood disease, renal and cardiac insufficiency, and X-ray treatment. His numerous acute attacks of «gout» do not support the diagnosis of arthritis urica. The latter is not uncommonly mistaken for calcinosis, especially in its circumscribed form, because the concretions in themselves may cause acute pain, swelling and redness; as they lie chiefly around the joints it may often be difficult and even impossible to distinguish between the two conditions.

The question now arises: Are this patient's acute attacks the result of calcinosis or arthritis urica? That the concretions have caused him acute pain we know from his second hospital period at Frederiksberg, where there were pain and tenderness at the middle of the right femur, where on his first hospitalization an infiltration was felt, from which later on a piece of calcium was removed at the Finsen Institute. It is quite possible that the periarticular deposits

may also be the cause of the other attacks. This being so, it cannot be decided whether arthritis urica alone caused the pains, nor can that possibility be dismissed.

Accordingly, we must assume that his acute »joint attacks» were caused especially, and perhaps exclusively, by the calcinosis; but there is the possibility that uric acid diathesis was a contributory cause.

About the year 1910 the term calcium gout was introduced by German authors [Minkowsky (28), Wichman (50), M. B. Schmidt (33) and Umber (40)] for circumscribed calcinosis. This was based in the first place on the exterior similarity of the calcium deposits with urate concretions in the case of arthritis urica, small hard nodules round the joints in or under the skin, fistules excreting chalky masses, acute attacks of pain, redness and swelling around the joints, and in the second place on the notion of a calcium diathesis of the same nature as uric acid diathesis. Weber (42) and Teissier (38), who were the first to describe calcinosis, have in fact drawn attention to these obvious comparisons. Thus there is a question of a parallelization of calcinosis with arthritis urica, not of a confusion or indeed of any close connection between the two diseases.

In a large number of the cases of calcinosis published in the literature determinations were made of the uric acid in the blood. A perusal of these results shows that the uric acid is nearly always normal.

Table 1 shows those cases where increased blood uric acid was found. The present author's cases are also included.

Eight out of ten cases were women in and after the climacteric period with circumscribed calcinosis. Moreover it is characteristic that as a rule there is only a single uric acid determination, or the uric acid was found to be slightly increased in one out of several tests. In no case did the increased uric acid occasion further examination; indeed, as a rule it is not commented upon, nor do the case reports suggest arthritis urica.

However, an exception must be made with Weil & Weissmann-Netter's (43) two patients, for whom the values seem to be the averages of several determinations. The patient with the much increased value of 67.8 mg % had once had acute pain and swelling of »la region mediotarsienne», without redness and without pyrexia.

At the time the case was regarded by her doctor as arthritis urica. Calcium was demonstrated only in the soft parts of the hands. Biopsy revealed no uric acid in the calcium deposits.

It will be seen that the woman with calcinosis circumscripta referred to in the present work (Table, No. 8) is of the same type as most of the post-climacteric women quoted earlier in the literature as having local calcinosis, without clinical arthritis urica, but with increased blood uric acid as the result of one test.

It is improbable that there was any uric acid diathesis in these cases; the cause of the momentarily increased blood uric acid must remain an open question. In two of the cases it may perhaps be explained by cardiac insufficiency.

In the case reported by Krauss (27) the diagnosis of calcinosis is unverified and doubtful. There were only two small concretions at one heel.

Constantly increased blood uric acid inconjunction with universal calcinosis as in our case is unique. Whether there is a pathogenetic connection or not cannot be determined. One might consider whether the calcium is not deposited in old deposits of urate. One weighty argument against this probability is the analysis of the two pieces of calcium, which contained no uric acid; no uric acid has ever been found in the deposits of calcium in calcinosis. An analysis of a fresh concretion might help to solve this problem.

The elucidation of these interesting points is hindered first and foremost by the fact that the individual observer sees only few instances of the disease. In future the blood uric acid should be determined several times in all cases of calcinosis.

Finally, there is the diagnosis of *hypogonadism*. As will be seen, the patient had high blood cholesterin, and the hormone analysis revealed increased gonadotropin secretion and reduced androgen secretion. (With the methods used here the normal values for men of this patient's age-group are  $< 50$  m.u. gonadotropin and  $\geq 20$  i.u. androgen [Hamburger (19) and Hamburger & Halvorsen (21)]. The blood cholesterin and hormone analysis give exactly the same values as those found in castrates and hypogonads. [See e.g. Teilum (37), Hart Hansen (22), Hamburger and al (19, 20, 21)].

On further examination with reference to hypogonadism the patient stated that he has not had parotitis, does not suffer from

excessive perspiration or heat, and that he is not depressed or nervous. Libido normal earlier, decreasing the last few years. Last coitus two months ago. Shaves every other day. Body hair scarcely reduced.

Physical examination: As already stated, of normal build and weight. Genitalia of normal development, no palpable atrophy of the testes. Prostate not definitely diminished. Skin fine and dry. Normal hairing of linea alba and pubes, but only sparse growth in axilla, while breast, thighs and legs have no terminal growth. Head hair natural. Standard metabolism normal, as already mentioned.

Thus the clinical examination revealed no particularly outstanding signs of hypogonadism, but after the laboratory finds described there can be no doubt of its presence. As we know, no characteristic »castrate type» can be set up, even for castrated males [Sand (32)].

In the literature the writer has found one case of calcinosis in a hypogonad male, described by Werther (49). This was a sixteen year old male with scleroderma and circumscribed calcinosis. He had no pubic hair, his voice was high and testes no more than bean-sized. Serum cholesterin was not determined.

In contrast to what is the case with uric acid, blood cholesterin is only rarely tested for in calcinosis. In some few instances it has been found to be high when the limit is somewhat arbitrarily put at 230 mg % (the methods of determination are usually not mentioned).

In the literature available to me I have found the following cases (Table 2). The author's own case is also included.

The first seven have the following features in common. A single determination showed a high cholesterin value in women during and after the menopause. In Wilson's case (51), however, there were several determinations. They all have calcinosis circumscripta.

There is no general agreement as to how high the blood cholesterin must be before there can be a question of pathologically increased values. Particularly in women during and after the menopause it is stated by some authors that the cholesterin was higher. Kaufmann & Mühlboch (26) in certain cases observed increased cholesterin during the physiological climacteric, and Bokelmann & Mühlboch (5) found an average increase of about

40 mg% after the age of fifty in the course of an investigation of serum cholesterin among women of various age groups. After roentgen castration there is a distinct increase of serum-cholesterin [Teilum (37)].

On this background most of the blood cholesterin values published are not remarkable. What is more, Ducasse's patient (11) and possibly Steinitz's (35), had a disease of the liver-bile passages.

In the patients of Wilson (51) and Weissenbach & al. (47) metabolism was normal. (In both cases the cholesterin values became normal under thyreoidin treatment). Taken as a whole, the authors were unable — or did not try — to find any explanation of the high cholesterin values (which, as already stated, may of course not be particularly remarkable, except for Wilson's (51) and Weissenbach & al.'s (47) cases).

This also holds good of the only case of calcinosis universalis, where Grenaud & Lescoeur (15) found 230 mg% in a nine-year old girl. These authors write: «Nous avons trouvé une hypercholéstérolémie marquée, sans pouvoir en tirer de conclusions.»

Although the number of those examined is not especially large, we may assume that high cholesterin values are scarcely the rule in calcinosis. The question then arises of whether a high serum-cholesterin value when found has any bearing on the calcium deposits. Cholesterin is readily deposited, as for example in the case of gall stone. Both Ducasse (11) and Weissenbach & al. (47, 48) found a very small quantity of cholesterin in the subcutaneous calcium nodules, but neither Steinitz (35) nor Wilson (51) found any at all. Nor was there any trace in our patient; and on the whole there is no cholesterin in the deposits, as is proved by the many analyses of concretions in cases of calcinosis.

Consideration has been given to the suggestion that high cholesterin values by radiation with ultraviolet rays might give rise to endogenous hyper-vitaminosis D, which causes the calcium to precipitate. Wilson (51), Weissenbach, Basch & Basch (44) and Grenaud & Lescoeur (15) have all gone into this suggestion, which however will hardly suffice as a general explanation of calcium deposits.

A final problem to discuss is that of whether hypogonadism bears any close relation to calcinosis.

The aetiology and pathogenesis of calcinosis are not known,

with the result that in the course of time investigators have turned their attention to various possibilities, one being disturbances of internal secretion.

In support of the suggestion of an hormonal pathogenesis it is said that circumscribed calcinosis occurs almost exclusively in females, and mostly during and after the menopause. Furthermore, there have been coincident occurrences of endocrine affections and calcinosis. There are reports of about ten cases of struma (see Steinitz (35)), a few with signs of hyperthyreoidism [Strauss (36), Durham (12), Garcin & al. (14)], and one or two with signs of hypothyreoidism [Guhrauer (17), Bertolotti (4)]. There are also cases of menstruation anomalies, especially amenorrhoea [see Weissenbach & al. (45)]. There are some few reports [e. g. Pontopidan (30)] of more or less marked »pluriglandular insufficiency» and infantilism [Bruusgaard (8), Holten (23) and Akobdzanzanz (1)].

From this one can merely conclude that there may be some correlation between calcinosis and certain changes in the endocrine system, but there is nothing to indicate any real causal connection; nor does there seem to be any question of correlation with a disturbance in any particular endocrine organ.

Finally, the picture of »pluriglandular insufficiency» and infantilism in the case of universal calcinosis may be due to the lowered general condition as a result of the calcinosis. Autopsy of three calcinosis cases [Versè (41), Hunter (25) and Durham (12)] revealed nothing abnormal in the endocrine organs.

On account of its relative rarity an endocrine disease can scarcely be any common denominator of calcinosis.<sup>1</sup>

Disturbance of the blood stream seems to be an important cause of calcinosis, at any rate in its circumscribed form. This is argued by the very marked correlation between calcinosis and an acrocyanotic condition and sclerodermia. The histological examina-

<sup>1</sup> Goldzicher (16) states that blood uric acid is increased in female eunuchoidism and female castrates, whereas uric acid is not mentioned in conjunction with the climacteric or in males. He also states that uric acid in the blood is constantly increased in *every* form of hypophysial affection, but perhaps especially in hyperpituitary conditions. In this he is in agreement with Rowe & Mortimer (31), who among 400 patients with various kinds of hypophysial affections found blood uric acid  $\geq 4$  mg % (excluding cases of nephritis and arthritis urica) in 31 per cent, with equal frequencies among hypopituitary and hyperpituitary cases. These investigations require further confirmation. The subject is but little examined, for which reason these findings have not been included in the present author's conclusions.

tion in our case supports unambiguously the view that it is a matter of calcium deposits in areas of degenerate connective tissue. As stated, the pathogenesis of calcinosis and the affections associated with it — scleroderma, dermatomyositis, etc. — is as yet unknown.

In conclusion it may be said to be very rare that true bone with cells and lamellae are formed in the case of calcinosis (fig. 5). Apart from the example described above it is mentioned only by Schulze (34), Becher (3), Breda (6) and Thygesen (39). It is also possible that it took place in one of Moberg's cases (29).

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## Appendix.

### Chemical Composition of »Calcium Deposits» from a Calcinosis Patient.

By

AKSEL TOVBORG JENSEN and JØRGEN E. THYGESEN.

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The analyses comprised two preparations: 9532 (left crus) and 9537 (right femur). No. 9532, which weighed 1.57 gramme, was a tough, brownish lump with a hard central core. As it was moist, it was dried in the exsiccator over sulphuric acid. After five days it was dry, and the tough outer part, consisting of muscle fibre etc., was cut away. There remained a stony core (weight 0.16 g), part of which was reduced in an agate mortar to a greasy paste. This paste was three times stirred with ether in the mortar and the ether decanted off after standing for a time. Between the washings the residue was further reduced, the resultant being a convenient white powder. During pulverization it was observed that the core was brittle and inelastic; it did not jump sideways during crushing as pieces of bone do. The ether extract from the core, like that from the excised soft parts, gave a negative reaction for cholesterolin a.m. Liebermann-Burchardt. Some mgs of the powder were used for making a roentgen diagram according to Debye-Scherrer. The diagram showed that the powder consisted of a colloidal apatite of a dispersion degree similar to that of bone phosphate.<sup>1</sup>

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<sup>1</sup> The calcium phosphate in the bones of vertebrates varies in dispersion degree in different bones and under different conditions, i. e. the apatite particles are not always of the same size, but the question has not been fully elucidated experimentally. The particles in the preparation examined are in any case, like those of bone phosphate, of colloidal dimensions and much smaller than those of the likewise colloidal hydroxylapatite  $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ , which can be prepared by precipitation in alkaline liquid at 100°.



The remainder of the core was chemically analysed after the method indicated by the authors for examining urinary concretions; this is justifiable, as it is the same substances that one would expect to find. The analysis gave calcium and phosphate, a little carbonate, faint trace of magnesium, but no oxalate or uric acid. Both crystallographically and chemically the core was thus very similar to bone.

No. 9537 weighed 0.03 g and gave 0.014 g powder. The x-ray diagram of it showed that this substance too was apatite, but of somewhat higher dispersion than No. 9532.

The Royal Veterinary & Agricultural College, Chemical Laboratory, Copenhagen.

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#### Summary.

The author reports on two cases of calcinosis, a typical circumscribed calcinosis in a woman and a universal calcinosis in a man. The latter had a constantly increased blood uric-acid value throughout thirty months of observation and numerous acute joint attacks. He also had high blood cholesterin, increased secretion of gonadotropin and decreased androgen excretion in the urine.

Cases of calcinosis with increased blood uric acid and with a high blood cholesterin content are collected from the literature and the bearing of these increased values on calcinosis is discussed.

Illustrations are provided in the form of three radiograms and two microphotographs.

In an appendix by Aksel Tovborg Jensen & Jorgen E. Thygesen is found a report of the chemical composition of calcium deposits from the universal calcinosis case.

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From Dep. E. (Infectious Diseases), Frederiksberg Hospital, Copenhagen.  
(Physician-in-chief: N. I. Nissen, M. D.)

## Sulfamethyltiodiazole.

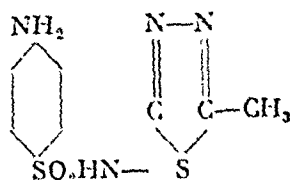
(«Lucosil».)

530 Pneumonic Patients treated with Chemotherapeutics.

By

N. I. NISSEN and KNUD SKADHAUGE.

(Submitted for publication December 17, 1942).



Sulfamethyltiodiazole (2-sulfanilamido-5-methyl-1, 3, 4-tiodiazole) was prepared first by Vonkennel & Kimmig (1940) in Germany and, independently of them, by K. A. Jensen & Possing (1941), in Denmark. Recently, in February 1942, experimental studies on the toxicology of this drug and its effect in vitro and in vivo against pneumococci and other microorganisms were reported by Andersen, Schmith & Søbye who also presented the first clinical experiences with this drug. They found its effect in vitro to be 4—8 times stronger than that of sulfapyridine. In vivo (experiments on mice), on the other hand, it was considerably less protective than sulfapyridine, possibly on account of its more rapid excretion and, consequently, lower concentration in the blood. Comparative studies on the toxicity of Lucosil, sulfapyridine and sulfathiazole showed Lucosil and sulfapyridine to be less toxic than sulfathiazole, because the latter has a greater tendency to crystalline precipitation in the urinary tracts. — *On treatment of 50 pneumonic patients Lucosil*

was found to be very effective and just as reliable as sulfapyridine (M & B 693) and sulfathiazole (Cibazol), and a daily dose of up to 6—7 g for 4—5 days (total dose of 10—44 g) gave practically no inconvenient by-effects. *As by-effects thus were far more infrequent with this drug than with the hitherto employed sulfonamides, the authors arrived at the conclusion that Lucosil is superior to sulfapyridine and sulfathiazole.*

Quite opposite results were recorded in April 1942 by Rune Frisk, in Sweden. He employed the same preparation and, like the above-mentioned authors, demonstrated that this substance is excreted considerably more rapidly than the other sulfonamides and, with the same dosage, its concentration in the blood is lower. Even with a higher dosage (2 g + 2 g + 1 g and so on every 4 hours) than usually employed for sulfonamide therapy in pneumonia he was not able to obtain a concentration of the drug in the blood sufficiently high for the therapeutic purpose, in his opinion. His material was rather small, comprising only 15 treated patients with acute infectious diseases. Of these patients, 11 pneumonics reacted satisfactorily to the treatment, while 2 showed no effect. In 50 % of the cases, however, the author found an increase in urinary non-protein nitrogen and oliguria, in 2 cases even in an alarming degree. *Frisk concluded that in Lucosil treatment with a sufficiently high dosage the risk of toxic kidney complications is too great, and that the substance, therefore, offers no therapeutic advantage over sulfathiazole.*

Finally, Alm has reported his employment of this drug in 7 cases of severe acute infectious disease in children, including Pfeiffer meningitis in one patient, with excellent results. The author emphasizes strongly that in comparison to sulfathiazole and sulfapyridine this drug is almost entirely free from by-effects.

#### Writers' Results.

When we decided to try out clinically the preparation designated as Lucosil<sup>1</sup>, the toxicity of sulfamethylthiodiazole and its effectivity in animal experiments had been elucidated adequately by Andersen, Schmith & Søbye (personal communication).  
*Material, Technique and Dosage.*

<sup>1</sup> We are obliged to Lundbeck & Co. for the generous supply of this drug.

From December 1941 to July 1942 all our patients with acute infections of the lungs and numerous other acute infectious diseases were treated with Lucosil. The present paper will deal only with the treatment of 132 pneumonic patients. As to the character of the material, the technique of treatment and examination together with dosage, the reader is referred to previous reports from this department on sulfonamide therapy. On the whole, the dosage for the various age-classes has been the same as given for sulfamethylthiazole and sulfathiazole treatment (Acta med. Scandinav. CIX, p. 417, 1942 and CXI p. 1. 1942) though a little larger for infants and young children, as illustrated by the following examples:

1) 3 months: 1 tabl. (0.5 g) +  $\frac{1}{2}$  +  $\frac{1}{2}$  and so on, every 4 hours; altogether 12 times = 3  $\frac{1}{4}$  g.

2) 7 months: 1 tabl. + 1 + 1 every 4 hours; altogether 18 times = 9 g.

3) 13 months: 1 tabl. + 1 + 1 every 3 hours the first day, then every 4 hours the 2<sup>d</sup> day and every 6 hours the 3<sup>d</sup> day, making a total of 9  $\frac{1}{2}$  g in 3  $\frac{1}{2}$  days.

4) Children over 2 years: 2 + 1 + 1 tabl. and so on every 4 hours for up to 4—5 days.

5) Children from 8 to 10 years: 3 tabl. + 1  $\frac{1}{2}$  + 1  $\frac{1}{2}$  and so on, or 3 tabl. + 2 + 1 and so on, for 4—5 days.

6) Children over 10 years were usually given adult dose: 4 tabl. + 2 + 2 and so on for 4—5 days, but with discontinuance of the night dose after 3 days.

This treatment is continued till a normal temperature is obtained, though not for more than 5 days. If a fall in temperature is not obtained after 48—92 hours, a change was made to another chemotherapeutic, as a rule sulfapyridine (M & B 693) just as in treatment with other sulfonamides.

For the sake of space we have omitted here to give a detailed tabulation of the patients similar to those presented in the earlier papers.

### *Therapeutic Results.*

A thorough comparison of the sulfamethylthiazole, sulfathiazole and Lucosil materials show no particular difference as to the age distribution of the patients and the pneumococcal types encountered (Table 2). On the other hand, the Lucosil material appeared

Table  
*Correlation of Therapeutic Results Obtained with Sulfamethylthiazole (SMT) and Sulfathiazole (ST)*

| Sulfamethylthiazole (SMT)<br>(Alfred Benzon) | No. of<br>patients | Died | Sulfathiazole (ST)<br>(Chemosept) |
|--|--------------------|------|-----------------------------------|
| SMT alone                                    | 55                 | 4    | ST alone                          |
| » + M & B 693                                | 13                 | 1    | » + M & B 693                     |
| » + serum                                    | 7                  | 1    | » + serum                         |
| » + serum + M & B 693                        | 2                  | 0    | » + M & B 693 + serum             |
| Total  | 75                 | 6    |                                   |
| Case mortality for: SMT alone, 7.3 %         |                    |      | Chemosept alone, 7.1 %            |
| » » » Total, 8.0 %                           |                    |      | Total, 8.5 %                      |

on the whole to include several more exhausted patients, on which account we now and then, especially in the beginning of the Lucosil period did not venture to omit replacing Lucosil with a preparation that had been tried out more extensively, in particular sulfapyridine (M & B 693) when 2—3 days' treatment failed to have the desired effect on the temperature. As a rule, however, the pneumonias which did not yield to Lucosil were found not to have any tendency to yield to other sulfonamides. The outcome of the Lucosil therapy as compared to the treatment with sulfapyridine, sulfathiazole and sulfamethylthiazole is evident from Tables 1 and 2 and Figs. 1 and 2.

Of the entire material 11 patients died:

1. Male, 3 months old, admitted on the 8' day of illness. No effect after two days' Lucosil therapy; then treatment with M & B 693 for two days, also without any effect. Autopsy: Pneumonia of the right upper lobe.
2. Male, 2 years old. Lucosil therapy from 4' to 6' day of illness, sulfathiazole from the 6' to 8' day, both remedies without any effect. Staphylococcus aureus was isolated from pleural effusion. Autopsy: Extensive pneumonia and beginning empyema.
3. Male, 50 years old. Pneumonia produced by Type 6. Lucosil therapy from the 9' to 12' day of illness, without effect. Autopsy: Bilateral bronchopneumonia.
4. Female, 50 years old. Type 3, bilateral bronchopneumonia + bronchiectasis. At first, good effect from Lucosil; subsequent, the patient died of gangrene of the lung.

1.

*methyllthiazole, Sulfathiazole, and Sulfamethylthiodiazole.*

| No. of patients      | Died | Sulfamethylthiodiazole (Lucosil) | No. of patients | Died |
|----------------------|------|----------------------------------|-----------------|------|
| 112                  | 8    | Lucosil alone                    | 109             | 5    |
| 3                    | 1    | " + M & B 693                    | 6               | 2    |
| 1                    | 0    | " + M & B 693 & ST               | 3               | 2    |
| 2                    | 1    | " + ST                           | 11              | 1    |
|                      |      | " + serum                        | 1               | 0    |
|                      |      | " + serum + M & B 693            | 1               | 1    |
|                      |      | " + serum + ST                   | 1               |      |
| 118                  | 10   |                                  | 132             | 10   |
| Lucosil alone, 4.6 % |      |                                  |                 |      |
| Total. 7.6 %         |      |                                  |                 |      |

5. Female, 63 years old, Type 10. At first, good effect from Lucosil; later relapse, in which M & B 693 and sulfathiazole were ineffective. Autopsy: Extreme toxic degeneration of the organs and myofibrosis of the heart.

6. Male, 64 years old. No pneumococcus type. Good effect from Lucosil; subsequently the patient died of intoxication and myocardial degeneration.

7. Female, 62 years old. No pneumococcus type. Sepsis, produced by non-hemolytic streptococcus. No effect from any of the chemotherapeutics employed. The patient died of endocarditis.

8. Male, 67 years old. No pneumococcus type. Good effect from Lucosil. The patient died of pulmonary embolism.

9. Female, 90 years old. Excellent effect from Lucosil. The patient died subsequently from cerebral hemorrhage.

10. Female, 74 years old. No pneumococcus type. Excellent effect from Lucosil. The patient died later from diverticulosis with perforation and peritonitis.

11. Female, 83 years old. No pneumococcus type. No effect from Lucosil; brief effect from M & B 693. She died of heart failure.

In previous studies concerning sulfathiazole and sulfamethylthiazole, the fall in temperature in the first 8 hours of treatment was less abrupt for these remedies than for sulfapyridine, possibly owing to a stronger antipyretic effect of the latter. The same applies to Lucosil, which shows even a little slower fall in temperature than obtained with sulfathiazole and sulfamethylthiazole (see Figs. 1 and 2), but this does not seem to influence the case mortality,

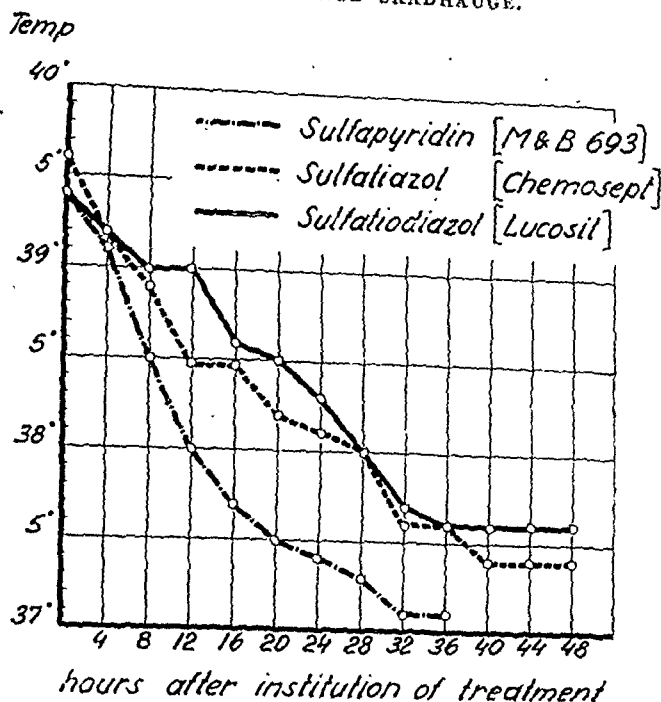


Fig. 1. Average temperature curves for Types 1, 2, 4 and 7 pneumonias treated with sulfapyridine (25 cases), sulfathiazole (19 cases) and Lucosil (20 cases) in the first 36—48 hours after the institution of treatment, with administration of the remedy every 4 hours. The temperature is measured every 4 hours.

which falls at the same level for this drug as for the other sulfonamides. So no particular difference can be demonstrated in the curative effect of Lucosil as compared to that of sulfathiazole and sulfamethylthiazole, and Lucosil may therefore be said to be fully equal to these two remedies.

Table 2 gives a survey of the treatment of pneumonias as carried out in Dep. E in the last 3 years.

Considering the case mortality (especially for columns 5 and 6, it is to be emphasized that a great many of these cases had been very severe, especially the secondary pneumonias in patients exhausted from their primary infectious disease. As mentioned already, the most severe cases, recorded in columns 5 and 6, were often treated successively with 2 or 3 sulfonamides. Taking the rate of the fall in temperature as a measure for the effect of the drug, the best effect was usually obtained with sulfapyridine; but often this remedy has failed. In several cases, no doubt, it was the combined chemo- and serotherapy that saved the life of the patient



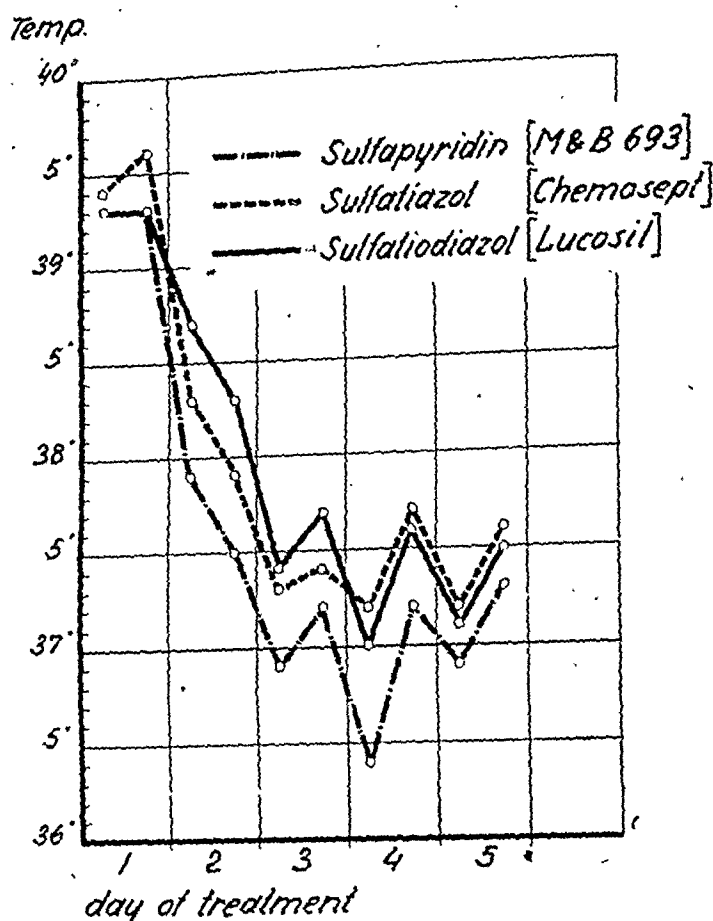


Fig. 2. Average temperature curves for Types 1, 2, 4 and 7 pneumonias under 5 days' treatment with sulfapyridine (24 cases), sulfathiazole (20 cases) and Lucosil (19 cases), with administration of the drug every 4 hours.

especially in cases of bacteremia and in pneumonias involving 2 and 3 lobes, in which the serum treatment still is valuable. It will further be noticed that the case mortality is greatest for the infants than for the pneumonias of Type 3. Note the high «lobe quotient» in columns 5 and 6, in which the case mortality was 17—27 %, and where it undoubtedly would have been over 50 % in the absence of specific therapy.

#### Toxic Complications.

A most conspicuous feature of the Lucosil therapy is the striking absence of inconvenient by-effects, notwithstanding the relatively large doses given to children. In 13 cases, vomiting was observed once or twice in 4—5 days of treatment, and a chemically demonstrable hematuria was found only in one case and lasted one day.

Table

*Results of the Treatment of Pneumonias with Sulfapyridine (M & B 693), Sulfamethylthiazole (Alfa. Benzon)*

|   |   | Sulfapyridine<br>(M & B 693) | Sulfamethyl-<br>thiazole<br>(Alfa. Benzon) |
|---|---|------------------------------|--|
| Age   | No. of patients treated                 | 174 (16)                     | 55 (4)                                     |
|   | < 1                                     | 19 (6)                       | 3 (1)                                      |
|   | 1—5                                     | 46 (1)                       | 7  |
|   | 6—14                                    | 19                           | 6  |
|   | 15—25                                   | 16                           | 8  |
|   | 26—45                                   | 17 (1)                       | 13   |
|   | 46—60                                   | 27 (1)                       | 6  |
|   | 60                                      | 30 (7)                       | 12 (3)                                     |
| No. of patients<br>with pneumo-<br>coccus types             | 1                                       | 11 (1)                       | 3  |
|   | 2, 4, 5, 7                              | 18                           | 4  |
|   | 3                                       | 18 (2)                       | 9 (2)                                      |
|   | 6, 19, 23                               | 36 (3)                       | 13 (1)                                     |
|   | Other types                             | 43 (6)                       | 15 (1)                                     |
| No pneumococcus types                                       |   | 48 (4)                       | 11   |
| Complications<br>on treatment in<br>No. of pts.             | Vomiting                                | 104                          | 20   |
|   | Exanthema                               | 1                            | 1  |
|   | Drug fever                              | 0                            | 0  |
|   | Hematuria                               | 8                            | 0  |
|   | Neuritis                                | 0                            | 0  |
|   | Severe hematological com-<br>plications | 0                            | 0  |
|   |   | 65 %                         | 38 %                                       |
| Complications<br>with pneumonia<br>in No. of pts.           | Bacteriemia                             | 0                            | 0  |
|   | Serous pleurisy                         | 10                           | 6  |
|   | Empyema. Abscess                        | 2                            | 1  |
|   | Endocarditis                            | 1                            | 0  |
|   | Meningitis                              | 0                            | 0  |
| No. of deaths   |   | 16                           | 4  |
| Pneumonia not cause of death in                             |   | 4                            | 0  |
| Real case mortality.  |   | 6.9 %                        | 7.2 %                                      |
| No. of lobes/No. of lob. pneum.                             |   | 98/92=1.1                    | 50/50=1.0                                  |
| No. of non-lobar pneum.                                     |   | 82                           | 5  |
| No. of complications with severe myocardiac<br>degeneration |   | 34                           | 12   |

The figures in parentheses indicate the number of deaths.

2.

jathiazole (Chemosept), Sulfamethylthiazole (Alfred Benzon) and Sulfamethyl-  
(Lucosil).

| Sulfathiazole<br>(Chemosept)                 | Sulfamethyl-<br>tiodiazole<br>(Lucosil)      | Combined                    |                            | Total                  |
|--|--|-----------------------------|----------------------------|------------------------|
|  |  | Chemo-<br>therapy           | + Chemo-<br>serotherapy    |                        |
| 112 (8)                                      | 109 (5)                                      | 40 (9)                      | 40 (7)                     | 530 (49)               |
| 5 (1)  | 5  | 5 (2)                       | 1                          | 38 (10)                |
| 25   | 37   | 7 (1)                       | 2 (1)                      | 123 (3)                |
| 20 (1)                                       | 14   | 3                           | 2                          | 64 (1)                 |
| 12   | 9  | 7                           | 5                          | 57 (0)                 |
| 15   | 9  | 8 (1)                       | 13 (1)                     | 75 (3)                 |
| 11 (1)                                       | 11 (2)                                       | 5 (1)                       | 10 (3)                     | 70 (5)                 |
| 24 (5)                                       | 24 (3)                                       | 5 (4)                       | 7 (2)                      | 102 (24)               |
| 10   | 6  | 2                           | 12 (3)                     | 43 (4)                 |
| 9  | 12   | 3                           | 16 (2)                     | 62 (2)                 |
| 8 (1)  | 10 (1)                                       | 0                           | 8 (1)                      | 53 (7)                 |
| 21 (2)                                       | 21   | 7                           | 3 (1)                      | 101 (7)                |
| 18 (3)                                       | 23   | 5 (2)                       | 1                          | 105 (12)               |
| 46 (2)                                       | 37 (4)                                       | 23 (7)                      | 0                          | 165 (17)               |
| 42 }<br>8 }<br>6 }<br>5 } 55 %<br>0 }<br>0 } | 13 }<br>0 }<br>0 }<br>1 } 13 %<br>0 }<br>0 } | 18<br>0<br>0<br>2<br>0<br>0 | 6<br>1<br>0<br>3<br>0<br>0 |                        |
| 0<br>14<br>1<br>0<br>0                       | 0<br>11<br>2<br>1<br>0                       | 1<br>1<br>3<br>0<br>0       | 3<br>9<br>0<br>1<br>2      | 5<br>51<br>9<br>3<br>2 |
| 8<br>2<br>5.4 %                              | 5<br>3<br>1.8 %                              | 9<br>0<br>22.5 %            | 7<br>0<br>17.5 %           | 49<br>9<br>7.5 %       |
| 74/70=1.1<br>42                              | 85/72=1.2<br>37                              | 34/25=1.4<br>15             | 56/36=1.6<br>4             | 397/345=1.15<br>185    |
| 15   | 12   | 7                           | 7                          | 88                     |

In no instance were there any symptoms of neuritis, drug fever or exanthema; nor did such complications appear in the numerous patients treated with Lucosil for other infectious diseases. This absence of by-effects makes Lucosil a valuable chemotherapeutic, and the experiences of this department in this respect are thus quite in harmony with those reported from the Sundby Hospital in contrast to those reported by Frisk.

### *Sulfamethyldiazole in the Blood and Urine.*

In the Scandinavian countries, studies on the absorptive and excretory aspects of sulfamethyldiazole have been carried out by Frisk and by Andersen, Schmith & Soby. After a single dose of 4 g by mouth, Frisk found the concentration of this substance in the blood to reach its maximum within two hours. After 10 hours only a trace of the substance remained in the blood. The acetylated part was the last to disappear from the blood. The degree of acetylation was found to be insignificant though increasing with decreasing concentration. Andersen, Schmith & Soby were able after ingestion of a single dose of 2 g of sulfamethyldiazole to demonstrate this substance in the blood 30 minutes after its intake, and it reached its maximum concentration after 2—3 hours. After 7 hours no trace of the substance was found in the blood. The degree of acetylation is given by these authors to be from 5 to 10 %.

The excretion of the substance with the urine proceeds very rapidly. After 6 hours Frisk recovered from 66 to 88 % of the ingested amounts; after 10 hours, from 84 to 95 %, with 3—9 % as acetyl derivate. The clearance is given to lie at a higher level than for the other sulfonamides, as a rule only from 10 to 15 % under the creatinin clearance.

Andersen, Schmith & Soby recovered in 3 cases from 85 to 100 % of the ingested drug in the urine, from 4 to 10 % of it as acetyl derivative.

On continual intake of this drug in the dosage generally employed — an initial dose of 2 g and after this 1 g every 4 hours — Frisk found the concentration in the blood 15 hours after the initial dose to vary between 0 and 3.6 mg for the total substance (averaging 1.58 mg %), and from 0 to 3.1 mg % for the free compound (averaging from 1.20 mg %). After 39 hours the concentration of the substance in the blood was practically the same.

Andersen, Schmith & Sæbye, employing the same dosage, likewise found the concentrations in the blood varying but low.

### *Writers' Investigations.*

The absorption and excretion of sulfamethyltiodiazole were examined by us by determining the concentration of the substance in the blood in 20 of the above-mentioned patients, and also intolerance tests with single or repeated doses by mouth carried out on normal subjects or persons suffering from some irrelevant disease.

For the analysis we employed the Frisk modification of Marshall's method with diazotization of the primary aromatic amino group and subsequent linkage to diethyl- $\alpha$ -naphthylamin under formation of a reddish violet dye.

The colorimetric determination was performed with a Pulfrich-Stufenphotometer with employment of Kleinküvette 50 mm and filter S. 53.

»Eich curves» were constructed for this drug after the same principal as for sulfathiazole (Buch, Engbæk & Nissen) by addition of known amounts of the substance to blood in which coagulation was prevented by addition of potassium oxalate.

Determinations were made of free sulfamethyltiodiazole as well as acetylated. Under uniform conditions as far as possible 4 adults (2 men and 2 women, from 28 to 34 years old) and 4 boys, aged from 5 to 10 years were given a single oral dose of 2 g of the substance (tablets). The tablets were given at 9 a. m. and the concentration of the substance in the blood was determined 2, 6, 8, 12 and 24 hours after their intake.

In 3 of the adults and in all of the children the concentration was found to be maximal 2 hours after the intake of the drug, whereas in one adult man, the maximal concentration was not reached till 6 hours after the intake.

In the adults the maximal concentration varied between 2.7 and 5.6 mg % of free substance, and from 3.7 to 6.2 mg % of acetylated + free substance.

In the children the values varied between 2.6 and 6.6 mg % of the free substance and from 3.6 to 7.6 mg % of acetylated + free substance.

After 8 hours, 3 of the adults and all 4 children showed a concen-

tration of the free substance less than 1 mg %; and after 12 hours, only free sulfamethyltiodiazole could be demonstrated in one of the adults.

In the 4 adults the blood still showed demonstrable amounts of the acetylated compound as long as 24 hours after the intake, while at this point of time no sulfamethyltiodiazole whatever could be demonstrated in the 4 children.

The excretion of the substance with the urine was followed in 5 cases after administration of varying amounts of the substance.

After a single oral dose of 2 g, altogether 90.8 % was recovered from the urine, 83.5 % of this in the form of free sulfamethyltiodiazole. As early as 3 hours after the intake, 66.9 % was excreted.

In 4 cases, from 6 to 25 g of the drug was given by mouth over a period varying from 2 to 5 days. In these cases from 62 to 97.6 % of the ingested amount was recovered in the urine. The degree of the acetylation varied greatly, from 0 to 25 %. As there was no reason in any of the 5 experimental subjects to suspect any impairment of the kidney function, it seems reasonable largely to attribute the wide variations in the amounts of the substance recovered to individual differences in its absorption.

No clearance determinations were carried out by the writers, but Frisk has found the clearance high, greater than for the other sulfonamides, as a rule only from 10 to 15 % under the creatinin clearance.

For comparison of these findings with the corresponding aspects of sulfathiazole, two adults (a man, 31 years old, weighing 66 kg, and a woman, 28 years old, weighing 59 kg) were given 2 g sulfathiazole by mouth and one week later 2 g sulfamethyltiodiazole, likewise by mouth. The findings are recorded in Figs. 3 and 4.

In one case, in which the assay of the concentration was carried out after 1 hour, the sulfamethyltiodiazole concentration was found to be maximal already at this point of time, whereas the maximal concentration of sulfathiazole was not reached till 4 hours later. In this case too, the sulfamethyltiodiazole concentration was higher than that of sulfathiazole.

In the other case the maximal concentration was reached for both substances within 2 hours.

In both cases no free sulfamethyltiodiazole could be demonstrated after 8 hours, and the amount of the total substance was

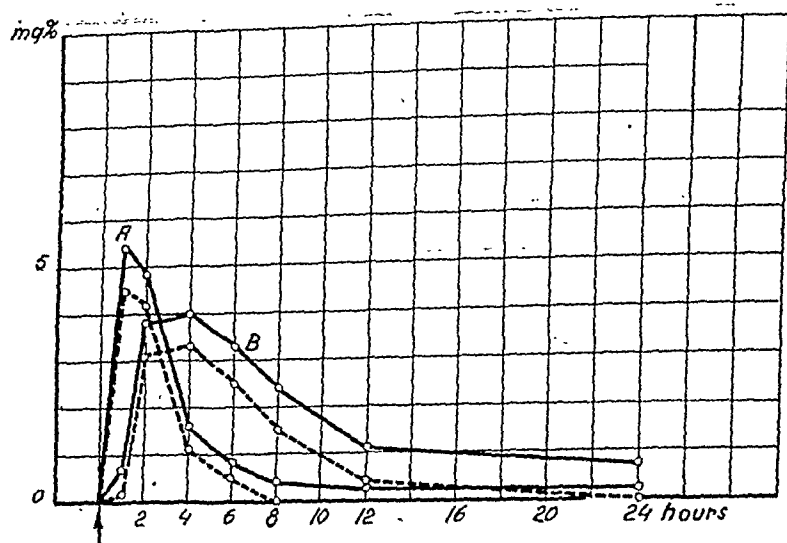


Fig. 3. Sulfamethylthiodiazole (A) and sulfathiazole (B) concentration of the blood after intake of 2 g of these drugs, respectively, in a normal man, aged 31 and weighing 66 kg.

found to be less than 1 mg %. At this juncture, however, the blood stain showed respectively 1.5 and 1.7 mg % free sulfathiazole and 2.3 and 3.1 mg % total sulfathiazole. In both of these cases, then, sulfamethylthiodiazole appears to have been excreted more rapidly than sulfathiazole.

For the sake of space we have omitted a tabulation of the blood concentrations observed in the 20 pneumonia patients. A survey of

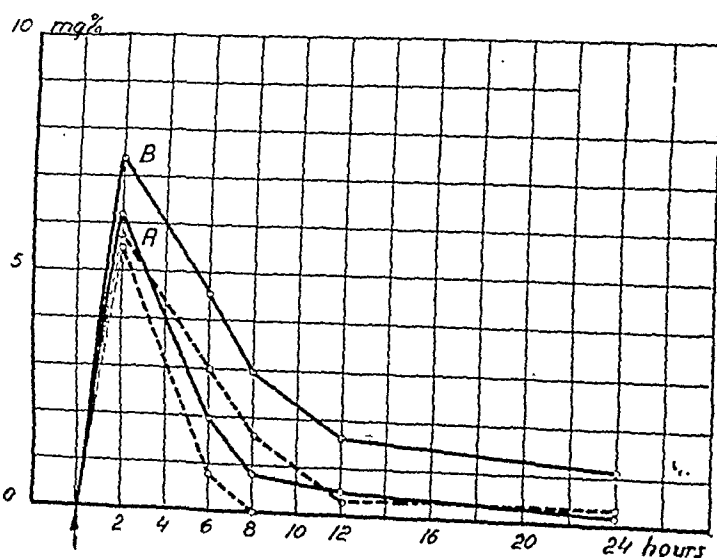


Fig. 4. Sulfamethylthiodiazole (A) and sulfathiazole (B) concentration of the blood after intake of 2 g of these drugs, respectively, in a normal woman, aged 28 and weighing 59 kg.

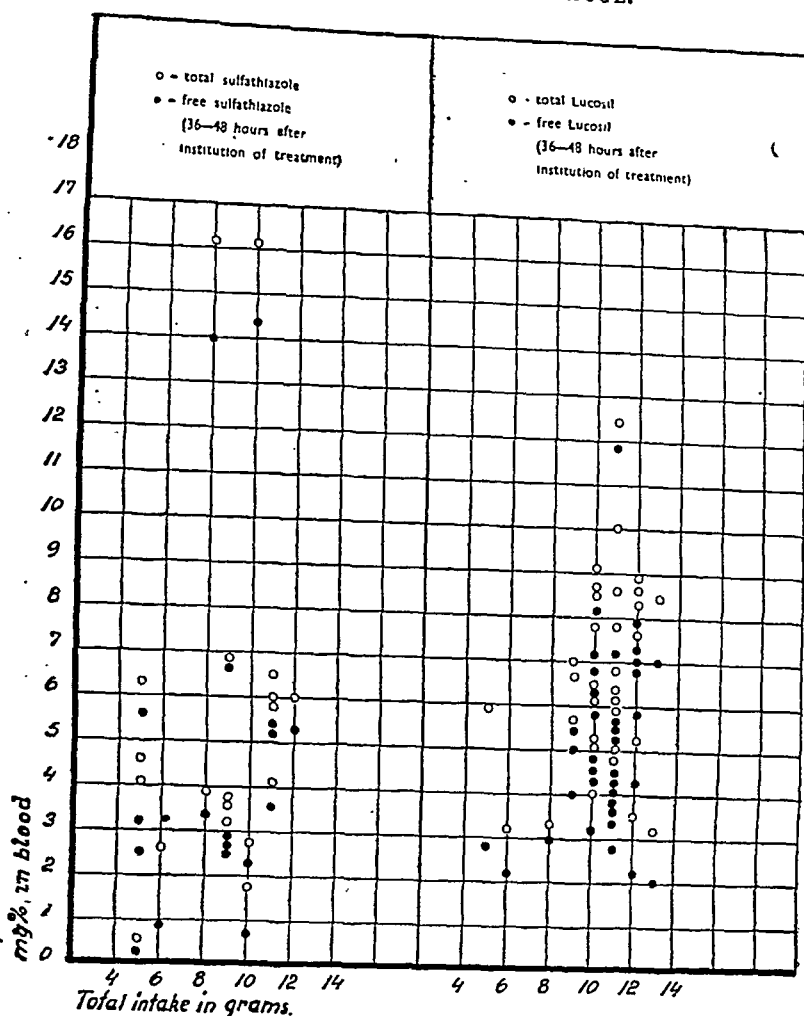


Fig. 5. Lucosil and sulfathiazole concentration of the blood, 36—48 hours after institution of the treatment.

the values especially in comparison to those obtained with sulfathiazole, observed after treatment for 36—48 hours, is given in Fig. 5.

In these 20 patients the concentration of the drug in the blood rose in the first 24 hours on an average to 4 mg % free substance and 5 mg % total substance, whereafter it fell in spite of the continued treatment. In 11 of the patients the Lucosil concentration of the blood 36 hours after the institution of the treatment, after a total intake of 11 g of the drug, was found to average 4.1 mg % free Lucosil and 4.8 mg % total Lucosil.

Under continual administration of the drug, the degree of ace-



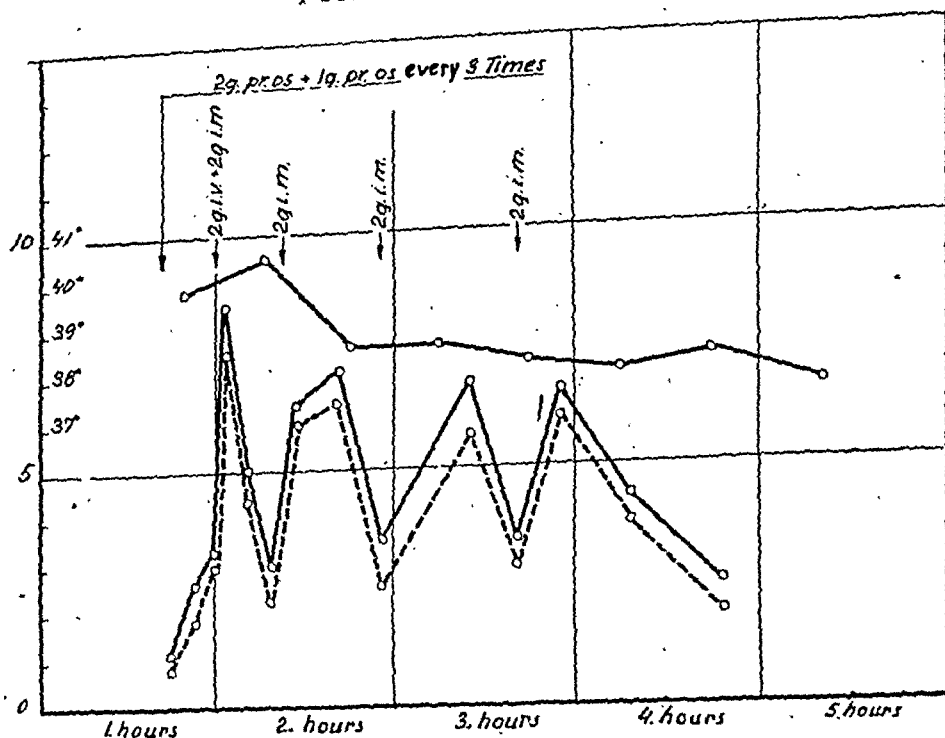


Fig. 6. Lucosil concentration of the blood under continual treatment with Lucosil by mouth as well as parenterally.

tylation has been varying greatly, as a rule increasing with decreasing concentration of the substance.

Two cases showed an abnormal rise in the Lucosil concentration of the blood:

In patient No. 2339/41, a woman, 50 years old, the Lucosil concentration of the blood after intake of 4 g was 8.7 mg % free and 11.0 mg % total Lucosil, increasing during the following 24 hours to 14.0 mg % free and 16.2 mg % total, with a dosage of 1 g every hour. This patient showed at the same time an increase in blood urea to 93 mg %, so that it appears as if the abnormal rise in the blood concentration may be attributable to impairment of the kidney function. In the other patient, No. 85/42, a man, 34 years old, the Lucosil concentration of the blood after administration of 6 g was 9.5 mg % free and 11.0 mg % total Lucosil, which in the following 24 hours increased to 14.4 mg % free and 16.2 mg % total. In this case no adequate explanation of the abnormal rise in concentration could be found.

In the case of another patient (1290/42) the drug was given exclusively by intramuscular injection, in the same dosage as employ-

ed for the peroral treatment. In this case the concentration kept at a level of 2 mg % free and 2.5—3 mg % total Lucosil. The neutral Lucosil solution (pH = 7.3—7.4) was employed for these injections. Each ampulla of 55 cm<sup>3</sup> of this solution contains 2 g of a complex ammonium salt of Lucosil. The injections produced no infiltration, but they gave some pain owing to the high osmotic pressure of the solution. Very likely this inconvenience may be avoided or diminished by dilution of the injection solution with an equal part of sterile water.

In one case a combined peroral and parenteral administration of the drug was employed (both intravenous injection and intramuscular). The findings are recorded in Fig. 6.

### Discussion.

Lucosil appears to be absorbed just as rapidly and completely as other sulfonamides.

The Lucosil concentration of the blood after a single dose given by mouth appears to reach the same maximal concentration as, for instance, sulfathiazole — and perhaps it reaches this concentration a little sooner ( $\frac{1}{2}$ —1 hour after intake of the drug). On the other hand, the excretion proceeds more rapidly than in the case of sulfathiazole.

With the same dosage, the blood Lucosil concentration under continual administration of the drug is on an average a little lower than that of sulfathiazole, probably because of its more rapid excretion.

Our studies thus appear essentially to agree with the work of Andersen, Schmith & Søbyè, whereas we have not found the same low Lucosil concentrations of the blood under continual treatment as reported by Frisk.

### Summary.

1. Lucosil (2-sulfanilamido-5-methyl-1,3,4-tiodiazol) is tried out clinically in 132 cases of pneumonia. The fall in temperature on treatment with Lucosil is distinctly slower than the fall obtained with sulfapyridine (M & B 693) and a little more protracted than the fall produced by sulfathiazole (Chemosept), but the three remedies appear to have quite the same curative effect.

The *by-effects* in Lucosil therapy are quite insignificant and distinctly less pronounced than those observed in treatment with sulfapyridine, sulfathiazole and sulfamethylthiazole, on which account Lucosil is to be characterized as a valuable chemotherapeutic.

A material of 530 cases of pneumonia treated specifically is presented here. Of these cases 450 were generally mild or moderately severe, and they were treated exclusively with chemotherapeutics, each group of patients being treated with one and the same remedy. The case mortality for these 450 patients was 4.3 %. The remaining 80 cases were all very severe, and these patients were treated successively with different chemotherapeutics or with chemo- + serotherapy. For these patients the case mortality was 17—22 %.

The Lucosil concentration of the blood and urine was examined in normal subjects and in 20 of the treated patients and the outcome was compared to the corresponding findings for sulfathiazole. The Lucosil concentration of the blood was found on the whole to be a little lower than that of sulfathiazole, and its excretion was considerably more rapid.

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From the Department of Hygiene and Bacteriology at the University of  
Upsala, Sweden (Director, Prof. J. Reenstierna).

## On peculiar corpuscles occurring in tuberculous material.

Preliminary note.

By

V. HALLBERG.

(Submitted for publication January 11, 1943).

During the three and a half years in which I have used the Nachtblau method for staining tubercle bacilli (1, 2) I have in tuberculous sputa and organs, as well as in different tissues from Schaumann's disease, been able to establish, from time to time, sparsely occurring, fairly large, peculiar corpuscles. They are more or less fusiform, and provided, at one or both ends, with something resembling a snout. Their surface is mostly covered with prickles, imparting to the whole a certain resemblance of young pine-cones (Figs. 1—3). These »cones», as we have been accustomed to call them, take, generally, neither the blue stain (Nachtblau) nor the counter-stain (pyronin, neutral-red, etc.), but assume a yellowish-brown colour of different shades. Sometimes, however, they take the counter-stain. The ring marking the snout of the »cone» is black, only occasionally blue. The prickles can be shed, and then the corpuscles assume a transparent, colourless appearance. In a few sputa have been observed transition forms between »cones» and corpuscles resembling those occurring in tissues of Schaumann's disease. It should furthermore be emphasised that the »cones» in tuberculous material generally occur in association with Koch's

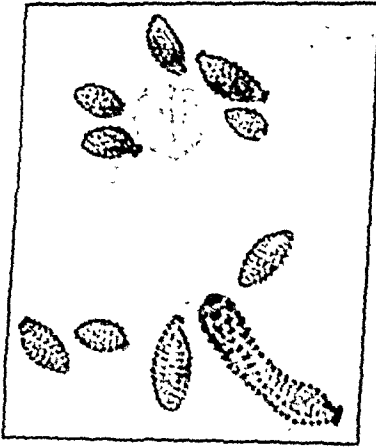


Fig. 1.

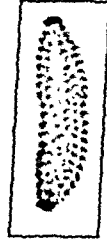


Fig. 2.

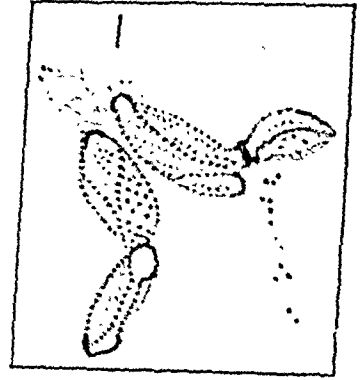


Fig. 3.

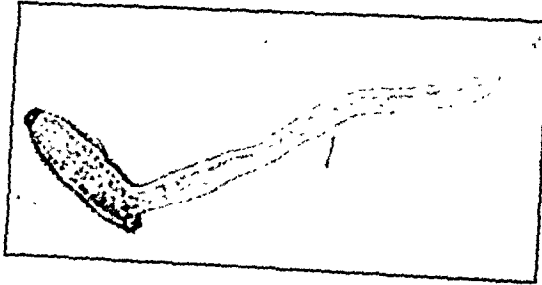


Fig. 4.

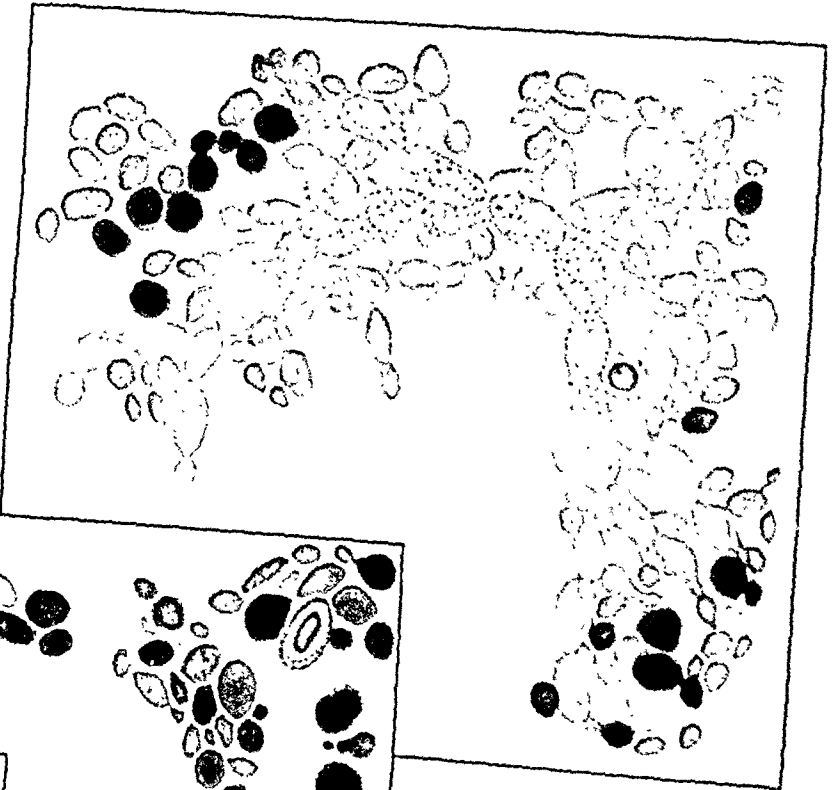


Fig. 5.

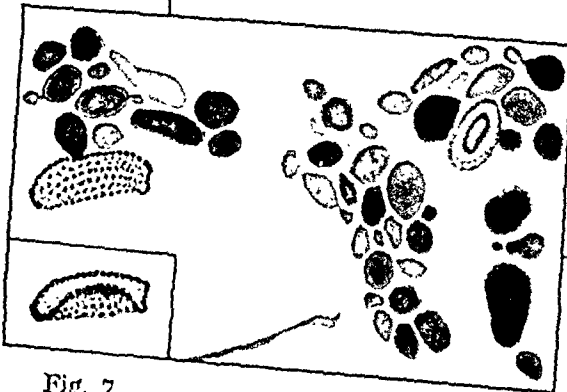


Fig. 6.

Fig. 7.

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### *Explanation of Plate.*

Figs. 1 and 2. Smears from the sputum of a patient suffering from pulmonary tuberculosis. Hallberg's simultaneous stain (Nachtblau and Bismarckbraun dissolved in anilin water). — The process will be published later. — Magnification, 1000 diameters.

Fig. 3. Smear from the sputum of another patient suffering from pulmonary tuberculosis. Besides the «cones» a Koch's bacillus is seen. Hallberg's simultaneous stain. Magnification, 1000 diameters.

Fig. 4. Smear from the sputum of a third patient suffering from pulmonary tuberculosis. A mycelial branch has grown out from a «cone». Also a Koch's bacillus is seen. Stain: Hallberg (Nachtblau-pyronin.) Magnification, 1000 diameters.

Fig. 5. Smear from a 40-days-old *single cell* culture (glycerin bouillon) of the Reenstierna tuberculosis fungus of 1912, isolated in 1939 from the sputum of a patient with tuberculous lung changes. Chains and agglomerations of fungus cells. Some of them have the normal appearance and colour (blue or red) but the majority are yellow, like «cones» and display most of their characteristics. But no distinct snout is seen. Stain: Hallberg (Nachtblau-fuchsin). Magnification, 1000 diameters.

Fig. 6. Smear from a 40-days-old *single cell* culture (glycerin bouillon) of the same fungus isolated in 1939 from the sputum of another patient with tuberculous lung changes. Here is seen a real «cone» with a snout at both ends, as well as a cleft stratified «cone» somewhat resembling corpuscles occurring in tissues from Schaumann's disease. Stain: Hallberg (Nachtblau-fuchsin). Magnification, 1000 diameters.

Fig. 7. From the same film. The double-snouted «cone» seen with another microscope adjustment.

(From the medical clinic, Karolinska sjukhuset, Stockholm. Head: Professor Nanna Svartz).

## **On the reproducibility of human gastric secretion after subcutaneous injections of histamine.**

By

**EBBE NYMAN.**

(Submitted for publication January 4, 1943).

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In an earlier work (1942) the author used histamine, injected subcutaneously, as a stimulator while testing the inhibiting effect of atropine on the human gastric secretion. Supported by his own experience and other investigations the author presumed, which will be further reviewed, that an equal dose of histamine, subcutaneously injected to the same subject under standard conditions, but at different times, will produce equally great volumes of secretion. To this, however, the important reservation must be made, that the time between the different tests must not be so long what any essential change in the functional state of the mucous membrane has time to enter. That the factor of time plays a special role under pathological conditions may be evident. A gastrically or ulcerously changed mucosa can not be supposed to have the same capacity of secretion for a longer space. The progress or regress of the pathological process may also be traced in the volumes of secretion. That the capacity of secretion of the normal mucous membrane also is a function of time is made evident by the investigations of Polland and Bloomfield (1929) and Ihre (1938), which show a negative correlation between volume of secretion and age. These proofs the common experience that the frequency of hypochylia and achylia increases with rising age.



the supposition that we observe the zone of activity that lies between the threshold concentration and the blood concentration, which causes a maximal response. It is to be considered about the subcutaneous injection of medium doses of an active substance that the blood concentration never becomes so high as happens with the momentary, intravenous injection, that one risks to obtain a concentration in the blood and the effect organ that goes beyond its ability to give a proportional response.

The second principal fact which in this case may influence the showing of an eventual reproducibility, is the technique of the recovery of the juice which must be as free from objections as possible. In the cases of normal or oppulent responses of secretion, the Lagerlöf-Ågren double tube has been used and shown itself to be practicable under normal conditions.

As has already been pointed out, the problem of the reproducibility of human gastric secretion, caused by histamine has met with fairly small interest in the literature. The scarce investigations, which have been made in order to explain the question, seem almost wholly to confirm the principally plausible presumption that a reproducibility under standard conditions really is present. Anyhow no investigations in the literature have been found, which directly deny this presumption.

Thus Polland states in an investigation of the effect of atropine on human gastric secretion, caused by histamine: »Previous studies in this laboratory (Sampson, J. P.: unpublished observations) have shown, that repeated injections of histamine that follow after the effect of a former injection has worn off, produce practically the same titrable acidity and volume response».

In the same manner Porter (1931) investigated the effect of atropine on human gastric secretion, caused by histamine. Even in this material was the reproducibility a direct assumption to account for the value of the results, when it was the matter of judging the effect of atropine. Like Polland Porter used a fractional aspiration by means of a Rehfuß-tube. The histamine was administered subcutaneously in a dose of 0.01 mg per kilo of body weight. In 4 cases the injection of histamine was repeated after an interval of 90 minutes, in 4 other cases the attempt was repeated on the following day. In both series the later curves of secretion were practically identical with the former. Both ways of proceeding

thus gave the same result, i. e. that two similar curves of secretion can be obtained from the same individual at the same or following day with a variation of the volumes of secretion amounting only to 5—10 per cent.

In his great work about the human gastric secretion Ihre (1938) has not explicitly taken a position with regard to the question on the reproducibility of secretion, caused by histamine. Nevertheless certain facts can be read out of his material that seem to deny a reproducibility. In one of his cases (no. 100) where the X-ray investigation showed a somewhat irregular mucosal relief though apparently not of such an extent that it justified a clinical diagnosis of gastritis, the secretion after histamine (0.10 mg per 10 kg of body weight) for 60 minutes at two times with an interval of 12 days showed 140 and 92.5 ml, in fact a considerable variation. In Ihre's normal material the 1 hour secretion after histamine in females was about 70 ml. In an other case (no. 68) with the diagnosis of chronic, hypertrophic gastritis the responses of histamine at 3 different occasions were respectively 103, 91.5 and 77 ml and the intervals of time resp. 4 and 18 days.

To make any conclusions concerning the reproducibility from investigations on a pathological material with long intervals, is of course not justifiable. On the other hand has Ihre to the author verbally pronounced as his opinion that the human gastric secretion, caused by histamine subcutaneously, is principally not able to be quantitatively reproduced. As the experiences of the author are in direct contrast to Ihre's opinion, they will be reviewed in the following. This especially as the problem, as has already been pointed out, is of great importance for comparative studies of the effect of different inhibitive drugs to human gastric secretion.

### Methods and results.

In 8 persons, most of whom having gastric or duodenal ulcers, has the secretion caused by histamine, subcutaneously injected (0.10 mg per 10 kilos of body weight) at two occasions of 24—48 hours interval been examined for 60 minutes after the injection. The juice has been recovered by means of a continuous suction with the Lagerlöf-Ågren double-tube, according to Ihre's advice provided with considerably enlarged openings on the gastric portion. The

power of suction was 35 mm of Hg. The saliva has been removed by letting the patient spit out with his head bent forwards and sideways. The tube has been inserted 2—3 hours before the experiment started, which always have taken place in the mornings in order to avoid rhythmically induced variations of the responses. Before the injection of histamine, the stomach and duodenum have been sucked empty for at least 15 minutes. The subjects have been chosen with the consideration of getting different great responses of secretion represented. The results are seen on the following table, which represents the total amount of the volumes of secretion for the two experiments in each subject.

| Case no. | Sex and age | Clinical diagnosis | Secretion in ml per 60 min. at the 1st experiment | Secretion in ml per 60 min. at the 2nd experiment | Diff. in per. cent. |
|----------|-------------|--------------------|---|---|---------------------|
| 1.       | ♀ 37        | Ulcus duodeni      | 76.0  | 82.0  | 8                   |
| 2.       | ♂ 25        | Healthy            | 94.0  | 98.5  | 5                   |
| 3.       | ♂ 22        | Anemia             | 145.0   | 139.5   | 4                   |
| 4.       | ♂ 35        | Ulcus duodeni      | 156.0   | 155.5   | 0                   |
| 5.       | ♂ 35        | Ulcus ventriculi   | 192.5   | 181.0   | 6                   |
| 6.       | ♂ 36        | Ulcus duodeni      | 207.0   | 209.0   | 1                   |
| 7.       | ♂ 46        | Gastritis          | 270.0   | 274.5   | 2                   |
| 8.       | ♀ 40        | Ulcus duodeni      | 289.0   | 276.0   | 5                   |
|          |             |                    |   | Mean diff.: 4 per cent                            |                     |

The comparison shows, that the reproducibility of the human gastric secretion, caused by histamine is exceedingly good in the tested cases, as the difference between two experiments in no case exceeds 10 per cent and in most cases in 5 per cent or less.

The concordance of two experiments in the same individual is not only reduced to a quantitative one. In order to get a detailed picture of the curves of secretion, the vessels of aspiration have been changed every 5th minute and the gastric juice from each such period has been thoroughly measured and titred separately. The titring has been performed with N/10 NaOH and with dimethylamidoazobenzole and phenolphthaleine as indicators. The results are exemplified by following two pairs of experiments.

## Case no. 3

| First experiment                              |                      |                  |                       | Second experiment                             |                      |                  |                       |
|---|----------------------|------------------|-----------------------|---|----------------------|------------------|-----------------------|
| Time in minutes after injection of histamine. | Gastric juice in ml. | Free HCl in Meq. | Total acidity in Meq. | Time in minutes after injection of histamine. | Gastric juice in ml. | Free HCl in Meq. | Total acidity in Meq. |
| 1—5   | 6.0                  | 14               | 36                    | 1—5   | 5.0                  | 16               | 32                    |
| 6—10  | 25.0                 | 46               | 58                    | 6—10  | 23.0                 | 82               | 96                    |
| 11—15   | 21.5                 | 96               | 106                   | 11—15   | 17.5                 | 110              | 122                   |
| 16—20   | 16.5                 | 134              | 140                   | 16—20   | 17.0                 | 114              | 126                   |
| 21—25   | 14.0                 | 132              | 138                   | 21—25   | 15.5                 | 120              | 128                   |
| 26—30   | 15.0                 | 128              | 134                   | 26—30   | 16.5                 | 122              | 130                   |
| 31—35   | 13.0                 | 136              | 144                   | 31—35   | 12.5                 | 124              | 132                   |
| 36—40   | 12.0                 | 126              | 134                   | 36—40   | 10.5                 | 132              | 140                   |
| 41—45   | 7.5                  | 130              | 138                   | 41—45   | 10.0                 | 132              | 140                   |
| 46—50   | 7.5                  | 130              | 138                   | 46—50   | 8.0                  | 108              | 118                   |
| 51—55   | 5.0                  | 108              | 116                   | 51—55   | 4.0                  | 108              | 116                   |
| 56—60   | 2.0                  | —                | —                     | 56—60   | 0.0                  | —                | —                     |

## Case no. 7

| First experiment                              |                      |                  |                       | Second experiment                             |                      |                  |                       |
|---|----------------------|------------------|-----------------------|---|----------------------|------------------|-----------------------|
| Time in minutes after injection of histamine. | Gastric juice in ml. | Free HCl in Meq. | Total acidity in Meq. | Time in minutes after injection of histamine. | Gastric juice in ml. | Free HCl in Meq. | Total acidity in Meq. |
| 1—5   | 8.0                  | 50               | 62                    | 1—5   | 13.0                 | 56               | 68                    |
| 6—10  | 13.5                 | 74               | 88                    | 6—10  | 15.0                 | 66               | 78                    |
| 11—15   | 20.0                 | 102              | 112                   | 11—15   | 22.5                 | 108              | 114                   |
| 16—20   | 29.0                 | 102              | 112                   | 16—20   | 30.5                 | 112              | 120                   |
| 21—25   | 32.5                 | 110              | 118                   | 21—25   | 33.0                 | 112              | 120                   |
| 26—30   | 32.5                 | 110              | 118                   | 26—30   | 32.5                 | 114              | 124                   |
| 31—35   | 29.0                 | 116              | 124                   | 31—35   | 30.0                 | 118              | 126                   |
| 36—40   | 27.0                 | 114              | 124                   | 36—40   | 24.0                 | 116              | 124                   |
| 41—45   | 23.0                 | 112              | 120                   | 41—45   | 21.5                 | 108              | 118                   |
| 46—50   | 24.0                 | 108              | 116                   | 46—50   | 18.5                 | 110              | 120                   |
| 51—55   | 18.0                 | 100              | 110                   | 51—55   | 17.0                 | 100              | 108                   |
| 56—60   | 13.5                 | 98               | 106                   | 56—60   | 14.0                 | 94               | 102                   |

Two two pairs of curves represent observations available for the whole material. In each 5 minute's period the conformity is very good concerning both quantity and acidity. The investigation highly supports the assumption that it is possible to reproduce the

human gastric secretion, caused by histamine at different occasions that lie *near each other in time*. Thereby it seems to be without importance if it is the secretion of a healthy or pathologically changed mucous membrane which is to be investigated.

### Summary.

As it is of certain importance to test the effect of drugs inhibitive to human gastric secretion, caused by subcutaneously injected histamine, the author has contributed to the knowledge of the reproducibility of this secretion. The investigation has verified the experiences that plead for the presence of such a reproducibility. On a material consisting of 8 cases, most of them suffering from ulcer, the gastric juice, caused by histamine, has shown itself not only being reproducible quantitatively with a variation below 10 per cent (mean 4 per cent) but the details of the curves have also shown a very good correspondance as to quantity and acidity.

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Aus der Medizinischen Abteilung des Kungl. Akademiska Sjukhus in Uppsala (Schweden). Direktor: Prof. Gustaf Bergmark.

## Über die Natur des normalen gelben Harnfarbstoffs Urochrom und seine Beziehung zum Uroerythrin.

Von

Dr. M. WEISS.

(Bei der Redaktion am 26. November 1942 eingegangen).

### I. Urochrom und Uroerythrin.

Die Farbe des normalen Harns hat zu allen Zeiten die Aufmerksamkeit der Aerzte auf sich gezogen. Thudichum<sup>1</sup> hat dem gelben Harnfarbstoff den Namen Urochrom gegeben. Obgleich einzelne Harnfarbstoffe schon vor dem Urochrom bekannt waren — so das von F. Simon<sup>2</sup> so bezeichnete Uroerythrin — so hat doch keiner für die Erkenntnis der Harnfarbe eine solche Bedeutung erlangt wie das Urochrom. Nach Thudichum hat sich Garrod<sup>3</sup> eingehender mit dem normalen gelben Harnfarbstoff beschäftigt. Die von ihm bei der Analyse der Harnfarbe angewandte Ammonsulfataussalzung ist zwar mit einem Verlust von etwa  $\frac{2}{3}$  derselben verbunden, doch war die Möglichkeit gleichgefärbte Filtrate hiedurch zu erhalten, ein Fortschritt. Aber eine quantitative Beurteilung der Urochromausscheidung war auf diesem Wege nicht möglich und so sind andere Forscher wieder zu einer Schätzung der Harnfarbe im

<sup>1</sup> Brit. Med. Journ., Bd. 2, S. 504, 1864.

<sup>2</sup> Handb. d. angew. Med. u. Chem., Bd. I., S. 342, 1840.

<sup>3</sup> Journ. of Phys., Bd. 21, S. 190, 1897 und Bd. 29, S. 335, 1903.

Originalharn zurückgekehrt (Pelkan,<sup>1</sup> Drabkin<sup>2</sup>). Damit war aber wieder die Gefahr der Mitbestimmung anderer Farbstoffe verbunden.

Seit der Entdeckung des Urochromogens<sup>3</sup>, welches von mir ursprünglich zum Urochrom in Beziehung gesetzt, später aber als selbständiges Chromogen anderer Art erkannt wurde<sup>4</sup>, hat die Urochromfrage mich andauernd beschäftigt. In früheren Arbeiten<sup>5</sup> habe ich betont, dass das Urochrom sehr labil ist und dem Untersucher förmlich unter den Händen verschwindet. Eine Erklärung hiefür konnte ich damals nicht geben. Im Lichte der neuen Untersuchungen sind diese Eigenschaften aber verständlich. Die von mir in dieser Arbeit entwickelte Auffassung der Beziehung des Urochroms zum Uroerythrin ist das Ergebnis einer vieljährigen Beschäftigung mit dem Harn; sie weicht jedoch von den bisherigen Anschauungen so stark ab, dass die allmähliche Entwicklung derselben in ihrem Werdegang beleuchtet werden muss. Seit Langem war mir folgende Reaktion des normalen Harns bekannt: Bringt man je 5 cm<sup>3</sup> in 3 gleiche Eprouvetten, giesst zur zweiten 1 cm<sup>3</sup> 10 %ige Lauge, zur dritten 5 Tropfen Eisessig, so tritt ein Farbenumschlag auf. Die Harnfarbe vertieft sich in der zweiten Eprouvette und erreicht mehr als das Zweifache der ursprünglichen Farbe, während sie in der dritten Eprouvette abblasst, manchmal mit einem Stich ins Rötliche. Diese Reaktion habe ich immer mit dem Urochrom in Zusammenhang gebracht, ohne sie jedoch erklären zu können. Nimmt man einen klar filtrierten, praktisch urobilinfreien norm. Harn und verdünnt ihn dreifach mit Wasser, so erhält man in der dreifachen Schichttiefe nicht mehr die Ausgangsfarbe, sondern man muss die vierfache Schichttiefe anwenden. Verwendet man aber statt Wasser ein farbloses Knochenkohle-Filtrat eines normalen Harns, so ist die Farbenintensität nach der Verdün-

<sup>1</sup> Journ. of Biol. Chem., Bd. 43, S. 237, 1920.

<sup>2</sup> » » » » Bd. 75, S. 443, 1927. Bd. 88, S. 433, 1930.

<sup>3</sup> Wr. klin. Woch., 1907, Nr. 33. — Med. Klin. 1910, Nr. 42.

<sup>4</sup> Das Urochromogen ist die Ursache der Ehrlich'schen und der phys. Diazo-reaktion des Harns, während Urochrom sich an dieser Reaktion nicht beteiligt. Urochromogen fällt beim längeren Stehen im Ammonsulfatfiltrat diazo-positiver Harne unter Nachdunkeln als Uromelanin aus, welches fälschlich mit dem Urochrom in Verbindung gebracht wurde. Das Uromelanin liefert PbS beim Kochen mit einer Spur Bleiacetat und Alkali, enthält also organischen S, während Urochrom keine Spur einer solchen Reaktion gibt.

<sup>5</sup> Die Farbstoffanalyse des Harns I und II, Bioch. Zeitschr., Bd. 102, S. 236 und Bd. 112, S. 88, 1920.

nung in dreifacher Schichttiefe dem Ausgangsharn gleich. Es tritt somit durch Wasserzusatz, also durch Veränderung der Ionen-Konzentration, eine Verminderung der Harnfarbe um  $\frac{1}{4}$  ein. Ein anderes Phänomen ergibt sich, wenn man 100 cm<sup>3</sup> des normal-sauren Harns eindampft. Der Rückstand in 20 cm<sup>3</sup> Wasser aufgenommen und klar filtriert, ist nicht mehr gelb, sondern orange bis rötlich und oft ist dabei ein Sed. lateritium vorhanden. Salzt man etwa 50 cm<sup>3</sup> eines rein gelben Harns ohne Urobilinabsorption mit Ammonsulfat aus und filtriert, so ist der mit Ammonsulfatwasser gewaschene Niederschlag auf dem Filter nicht, wie es der gelben Harnfarbe entsprechen würde, gelb, sondern gelbbraun bis rötlich, während das Filtrat rein gelbe Färbung zeigt. Der grössere Teil der Harnfarbe geht dabei durch die Aussalzung verloren. *Die Fällbarkeit durch Ammonsulfat ist aber eine dem Uroerythrin zukommende Eigenschaft.* Löst man einen solchen Niederschlag in Wasser, so zeigt er mehr oder weniger deutliche Gelbfärbung, die aber schwächer ist, als es der nach dem Filtrat beurteilten Farbenverminderung entspricht. Von einem Gesamt-Farbwert von 10 wurden in einem meiner Versuche im Ammonsulfatfiltrat wiedergefunden 4, im Ammonsulfat-Niederschlag 2. Wohin sind die verlorenen vier Teile des Farbwerthes gekommen? *Sie sind verschwunden, weil sie nur durch die eigenartige Ionen-Konzentration des Harns zustande kamen.* Fügt man zu einer Lösung des Ammonsulfat-Niederschlags etwas Lauge, so erhält man nur eine schwach grüngelbe Färbung, weil der Farbstoff bei der Ausfällung denaturiert wird. Dagegen behält das Ammonsulfatfiltrat nicht nur die ihm zukommende reine Urochromfärbung, sondern man kann in ihm auch die Alkalireaktion nachweisen, wenn man die Störung durch das Salz ausschaltet, indem man ein Alkoholextrakt nach Garrod herstellt (4 Teile des Filtrats plus ein Teil konz. Alkohols im Schütteltrichter ausgeschüttelt). Das Extrakt gibt nach zweifacher Verdünnung mit Wasser Grüngelbfärbung bei Alkalizusatz. Eine weitere Tatsache lenkte die Aufmerksamkeit in die gleiche Richtung. *Die Harnfarbe kann bei ein und demselben Menschen schon im Laufe eines Tages von reinstem Gelb bis Orange wechseln.*

Ich habe lange gezögert der Frage näherzutreten, ob zwischen dem Uroerythrin und dem Urochrom genetische Beziehungen bestehen. Hat doch Garrod z. B. erklärt, dass im normalen Harn nur so kleine Spuren von Uroerythrin vorkommen, dass sie nicht zur Farbe desselben beitragen.



Aber die Zahl der Argumente, die in diesem Sinne sprachen, war so gross und das Urochrom selbst noch so problematisch, dass ich mich der Prüfung der Frage nicht entziehen konnte. Von allem Anfang war es mir klar, dass die Beweisführung für die nahe Beziehung zweier anscheinend so vollkommen verschiedener Farbstoffe nicht leicht sein würde. War es doch hierzu notwendig einerseits aus Uroerythrin Urochrom, andererseits aus Urochrom Uroerythrin zu erzeugen. Hiefür den endgiltigen Beweis durch die Analyse beider Körper zu liefern, war ausgeschlossen bei der gegenwärtigen Unmöglichkeit diese Farbstoffe vollkommen rein zu erhalten. Doch sind einige Reaktionen derselben so sinnfällig, dass diese Beweisführung vorläufig dahingestellt bleiben kann.

In einer meiner früheren Arbeiten<sup>1</sup> findet sich folgender Satz: »Die Farbe des Urochroms ist von der Ionen-Konzentration ausserordentlich abhängig; sie ist beim unveränderten Farbstoff bei saurerer Reaktion blassgelb, bei alkalischer aber grüngelb.« Übergiesst man ein Sed. lat. mit einer Alkalilösung, so erhält man ein grüngelbes Filtrat. Verwendet man schwaches Alkali, so ist die Intensität dieser Verfärbung schwächer, aber noch immer nicht so, dass sie der gelben Urochromfarbe entspricht. Nimmt man aber statt Alkali ein farbloses Knochenkohle-Filtrat, so erhält man nach längerer Einwirkung rein urochromgelbe Färbung. Der normale Harn verhält sich in Bezug auf seine Ionen-Konzentration eigenartig. Trotz saurer Reaktion gegen Lakmus hat er doch auch Eigenschaften eines Alkali, die ihn z. B. befähigen, Harnsäure in Lösung zu halten. Das farblose Knochenkohle-Filtrat behält diese Eigenschaft und wirkt daher dem Uroerythrin gegenüber wie ein sehr schwaches Alkali. *Es vermag dasselbe mit der gleichen Farbe zu lösen wie es im normalen Harn selbst in Erscheinung tritt, nämlich als Urochrom.*

Bei den Versuchen zur Darstellung von reinem Urochrom respect. Uroerythrin zur quantitativen Bestimmung des Farbstoffs aus seinem Alkaliwert (s. Kap. II) wurde eine grössere Menge von harnfrei gewaschenem Sed. lat. in heissem Wasser gelöst, die trübe Lösung mit der vierfachen Quantität konc. Alkohols versetzt und filtriert. In der klaren, orangefarbenen, alkoholisch-wässrigen Uroerythrinlösung wurde zunächst der Alkaliwert bestimmt<sup>2</sup>. Von dieser Lösung wurde ein Teil abgedampft und gewogen. Um jedoch harnsäurefreie Substanz zur Wägung zu erhalten, wurde

<sup>1</sup> Die Farbstoffanalyse des Harns, I, l. c.

<sup>2</sup> Ein Überschuss von Alkali muss hier vermieden werden, um den Farbstoff nicht zu zerstören.

der erste rein uroerythrinrote Rückstand in warmem Wasser quantitativ gelöst, das erkaltete Filtrat abgedampft und wieder gelöst, bis beim Erkalten kein Niederschlag von (farbloser) Harnsäure mehr ausfiel. Schon nach dem zweiten oder dritten Abdampfen der wässrigen Lösung *hat sich der ursprünglich rein orangerote in einen gelben Rückstand verwandelt*, der ebenso wie seine Lösungen in warmem Wasser Urochrom entsprach<sup>1</sup>.

Das Umgekehrte, aus Urochrom Uroerythrin bezw. dem Uroerythrin entsprechende Reaktionen zu erhalten, war weniger leicht. Durch Abdampfen normaler Harne kann man, wie erwähnt, die Uroerythrinfarbe und häufig auch ein Sed. lat. erhalten. *Dieser Umschlag einer gelben Farbe ins Rötliche wäre für einen genuin gelben Farbstoff bei seiner Konzentration unverständlich.* Behandelt man ein Sed. lat. mit 5 %iger Lauge, so erhält man die bekannte grüngelbe Färbung, die allmählich in Grüngelb übergeht. Die gleiche grüngelbe Färbung sieht man, wenn man urobilinfreie, urochromreichere Harne mit Alkali versetzt.

Am reinsten präsentiert sich das Urochrom im Ammonsulfatfiltrat des normalen Harns. Hier finden wir die Eigenart der Urochromfarbe besonders ausgeprägt, weil 1. durch die Ammonsulfataussalzung alle rötlichen Farbstoffe beseitigt werden, 2. weil Harnsäure ausgefallen ist. Lässt man ein solches Filtrat einige Stunden stehen, so trübt sich dasselbe oft durch ausfallendes Urochrom, welches, obgleich aus rein gelber Lösung ausgefallen, schon eine rötliche Farbe hat, weil die gelbfärbenden Alkali-Ionen darauf nicht mehr einwirken. Der aus einem gelben, klaren Ammonsulfatfiltrat ausfallende Farbstoff haftet manchmal der Wand des Gefäßes fest an und man kann am nächsten Tag klar abgiessen und das Gefäß mit Wasser harnfrei waschen. Der aus einer grösseren Menge von norm. Ammonsulfatfiltrat ausgefallene und der der Glaswand anhaftende Farbstoff kann mit heissem Wasser teilweise in Lösung gebracht und mit Amylalkohol extrahiert werden. Das Extrakt zeigt orange Färbung und spektroskopisch eine links schärfer begrenzte Absorption etwa zwischen Wellenlänge 540 bis 525, eine geringe Aufhellung danach, dann Verdunkelung des rechten Spektralteils bis etwa 485, ohne eine Spur eines Urobilinbandes, eine schwache Aufhellung im Violett (ähn-

<sup>1</sup> Die Rotfärbung des Urochrom-Uroerythrins kam daher durch die Verbindung mit Harnsäure zustande.

lich der Luteinabsorption) und bei etwa 450 beginnende totale Verdunkelung. *Dies ist aber die von Mc Munn und Garrod beschriebene Absorption des Uroerythrins.*

Uroerythrin gibt mit konz. Schwefelsäure tief rote Färbung. Die gleiche Färbung erhält man nicht nur mit dem ausgefallenen roten Farbstoff, *sondern auch mit allen Urochromlösungen, insbesondere auch mit dem Garrod'schen Extrakt.* Das spektroskopische Verhalten ist analog dem mit Uroerythrin selbst durch Behandlung mit Schwefelsäure erhaltenen Bild: Eine unscharf begrenzte, wenig beständige Absorption im Orange, eine darauf folgende, schmale Aufhellung und Verdunkelung oder Verschattung des übrigen Spektralgebiets.

Es war daher möglich, aus gelbem Ammonsulfatfiltrat Uroerythrin und durch Einwirkung von Schwefelsäure auf dieses sowie auf gelbe alkoholische Urochromlösungen die gleiche Farbe und die gleiche Absorption zu erhalten, wie sie durch Einwirkung desselben Reagens auf Uroerythrin selbst entsteht. *Damit war die Beweiskette für die Beziehung des Urochroms zum Uroerythrin geschlossen.* Schon jeder normale Harn enthält demnach eine gewisse Menge Uroerythrin, welches sich bei der ihm eigenen Bivalenz seiner Reaktion mit der normalen gelben Harnfarbe löst (Urochrom). Je grösser die Uroerythrinmenge ist, welche ein Harn zu lösen hat, umso weniger ist er im Stande mit den ihm zu Gebote stehenden alkalischen Valenzen das Uroerythrin in Urochrom zu verwandeln und umso mehr tritt die Orange- bis Rotfärbung gegenüber der Gelbfärbung in den Vordergrund. Dies ist besonders beim Fieberharn der Fall, wo nicht nur die absolute Uroerythrinmenge steigt, sondern auch die Harnsäure zuzunehmen pflegt, wodurch seine Lösungskapazität für Uroerythrin doppelt leidet. Das Uroerythrin fällt dann auch leicht bei der Abkühlung des Harns in Verbindung mit Harnsäure aus.

Die Identität zwischen Urochrom und Uroerythrin macht es verständlich, dass ein so regelmässig im normalen Harn vorkommendes Stoffwechselprodukt bei so vielen Krankheiten anscheinend völlig verschwindet und wir an dessen Stelle Uroerythrin antreffen. Mit zunehmender Besserung, wobei der Uroerythringehalt abnimmt, tritt die normale gelbe Harnfarbe wieder in ihre Rechte. Die Beweiskraft dieser Argumente erfährt aber die stärkste Stütze dadurch, dass wir den Farbstoff in den normalen Urochromharnen auf die-

selbe Art quantitativ bestimmen können, wie in den roten Uroerythrinharnen. *Es wird deshalb für den fallweise als Urochrom in Erscheinung tretenden Uroerythrinfarbstoff die Bezeichnung Urochrom-Uroerythrin vorgeschlagen.*

## II. Die quantitative Bestimmung des Urochrom-Uroerythrins.

Die meisten in der Literatur angegebenen Vergleichsflüssigkeiten zur Bestimmung der Harnfarbe enthalten Echtgelb<sup>1</sup>. Drabkin hat seine Vergleichslösung aus basischem Alizarin und Anilinorange hergestellt. Keine der künstlichen Farbmischungen entspricht regelmässig der Harnfarbe. Ich habe einen neuen Weg eingeschlagen, der die wichtigste Eigenschaft des Urochrom-Uroerythrins, die grüngelbe Färbung bei Alkalizusatz zum Ausgangspunkt der Bestimmung macht. Durch die hiedurch eintretende einheitliche Färbung wird ein wesentlicher Fehler aller früheren Bestimmungen ausgeschaltet, *die Farben des saueren und alkalischen Harns gleichzusetzen*. Als Vergleichslösung verwende ich folgende Mischung der leicht wasserlöslichen Oswald'schen Farbenzusammenstellung<sup>2</sup>:

|  |                    |
|--|--------------------|
| Oswald Gold 0.2 : 100 H <sub>2</sub> O, 22 × verdünnt..... | 55 cm <sup>3</sup> |
| » Grün 0.1 : 100 H <sub>2</sub> O, 5 × verdünnt.....       | 5 cm <sup>3</sup>  |

Diese Farbmischung ist gelb und hat den grünlichen Stich, der den Alkali-Lösungen des Urochrom-Uroerythrins in stärkerer Konzentration eigen ist. Sie stellt die Haupt-Standardlösung vor. Den in 100 cm<sup>3</sup> dieser Lösung enthaltenen Farbwert habe ich 10 gleichgesetzt. Um auch Bestimmungen bei schwächeren Harnfärbungen vornehmen zu können, habe ich noch eine zweite Farbmischung hergestellt, deren Wert die Hälfte, also 5 beträgt und in welcher das Grün fehlt:

Oswald Gold 0.2 : 100 H<sub>2</sub>O, 20 × verdünnt 20 cm<sup>3</sup> + 21 H<sub>2</sub>O = 41 cm<sup>3</sup>.

Beide Standardlösungen sind im Dunkeln haltbar; sie werden in planparallele Flaschen eingefüllt. Der Vergleich erfolgt mit freiem Auge bei Tageslicht in gleichen Flaschen, von denen, wenn nötig,

<sup>1</sup> Klemperer, Berl. klin. Woch., 1903, S. 313.

<sup>2</sup> In jeder Farbwarenhandlung zu erhalten.

2—3 hintereinander untersucht werden. Da jeder Harn zumindest Spuren von Urobilin und Porphyrin enthält, so müssen diese Farbstoffe zunächst beseitigt werden; ist der Harn durch ausgeschiedenes Sed. lat. getrübt oder hat sich ein derartiges Sediment schon abgesetzt, so wird umgeschüttelt. Dann werden 10 cm<sup>3</sup> 2, 3 oder mehrmal mit Wasser verdünnt, wodurch häufig schon Lösung der Trübung erfolgt; man kann durch leichtes Erwärmen die Lösung befördern.

Der Vorgang gestaltet sich folgendermassen: 20 cm<sup>3</sup> oder ein Multiplum des Harns, resp. zumeist seiner 2—3fachen Verdünnung werden mit 1 cm<sup>3</sup> oder einem Multiplum Eisessig (bei starker Alkalescenz mit dem Doppelten) und 5 cm<sup>3</sup> resp. dem Multiplum Amylalkohol im Schütteltrichter gut ausgeschüttelt. Man lässt die Mischung sich absetzen, die Harnflüssigkeit abfliessen, fügt ein wenig Talk hinzu, schüttelt durch und filtriert. Durch den Amylalkohol bei essigsaurer Reaktion wird Urobilin und Porphyrin extrahiert. Kleine Reste dieser Farbstoffe oder das selten vorkommende Uroporphyrin werden später beim Talkzusatz adsorbiert. Der Amylalkohol nimmt auch eine Spur Urochrom-Uroerythrin auf; dieser Verlust beträgt etwa 5 %, was ohne Weiteres vernachlässigt werden kann. Die Extraktion beigemengter Farbstoffe — dasselbe gilt vom Bilirubin — ist umso besser, je stärker der Harn mit Wasser verdünnt wird und wir können leicht auch mässig gefärbte normale Harnen schon zweimal verdünnen. Über 5malige Verdünnung brauchen wir nur selten auch bei stark ikterischen Harnen hinauszugehen. Das Talkfiltrat<sup>1</sup> wird mit 10%iger Lauge versetzt, in die planparallele Flasche oder Flaschen filtriert und der Urochrom-Uroerythrinwert durch Vergleich mit der Standardlösung 10 oder 5 bestimmt.

Eine Voraussetzung für das Gelingen der Bestimmung ist, dass der Harn frei ist von Medikamenten, besonders der Salicylgruppe, welche sich selbst durch Alkali gelb färben; dies erkennen wir durch die Eisenchloridprobe. Daher sollen derartige Medikamente einige Tage vorher nicht verwendet werden. Azeton oder Azetessigsäure stören aber nicht. *Der Harn darf ferner auch noch keine Nitrite enthalten.* Nitrite und Essigsäure erzeugen Farbenzunahmen, die einen höheren Farbstoffgehalt vortäuschen können. Eine Benzidin-Eisessiglösung erzeugt in Nitriharnen Rotfärbung; da Nitrite die Ehrlich'sche Aldehydprobe hemmen, so kön-

<sup>1</sup> Talkfiltrate, welche in tieferer Schicht noch Andeutung einer Urobilinbande zeigen, können wir durch wiederholtes Ausschütteln mit Talk urobilinfrei machen.

nen wir Harne mit einer deutlichen Urobilinogen-Reaktion von vornherein als nitritfrei ansprechen. Um Nitritbildung, welche zumeist sekundär ist, zu verhindern, empfiehlt es sich zu dem zu sammelnden Harn schon in das erste Gefäss etwas Chloroform zu geben und ebenso in das Glas, in welchem er zur Untersuchung kommt.

Dass Rhabarber den Harn färbt, war schon den alten Aerzten bekannt. Dasselbe gilt auch von Phenolphthalein und anderen Laxantia; ebenso sieht man oft Rotfärbung des Harns nach dem Genuss von roten Rüben. Eine Fehlerquelle kann die Anwesenheit von Alkaptochromogen bilden. Alkapton selbst bzw. Homogentisinsäure kommt bei der grossen Seltenheit der Alkaptonurie nicht in Frage. Der in der gleichen Weise verdünnte und mit Eisessig versetzte Harn wurde in einer Reihe von normalen und pathologischen Fällen vorher mit Aether extrahiert. Die Ausschüttelung des Aethers mit einer kleinen Menge Alkali ergab zumeist nur eine Spur Gelbfärbung, welche bei der Bestimmung nicht in Betracht kam. Mitunter war aber eine grössere Menge von Farbstoff nachweisbar. Die Verfolgung dieser Alkaptochromogene ergab, dass sie exogenen Ursprungs waren und aus Beeren sowie Obst stammten. Sie lassen sich jedoch durch Aether gut ausschütteln. Die beschriebene Bestimmung wurde zumeist mit einer vorherigen Aetherextraktion kombiniert, welche in den folgenden Beispielen nicht besonders angeführt ist.

1. M. W., 63 J., gesund, Harn-Tagesmenge 700 cm<sup>3</sup>, sauer, spez. Gew. 1025, nitritfrei. Der Harn ist leicht von Uraten getrübt. 10 cm<sup>3</sup> des gut durchgeschüttelten Harns wurden zweimal mit Wasser, also auf 20 cm<sup>3</sup> verdünnt, wodurch sich die Trübung aufhellte. Zu den 20 cm<sup>3</sup> kamen 1 cm<sup>3</sup> Eisessig und 5 cm<sup>3</sup> Amylalkohol im Schütteltrichter. Die scharf abgesetzte Harnflüssigkeit wurde abgelassen, mit etwas Talk versetzt, geschüttelt und filtriert. Das Filtrat betrug 18 cm<sup>3</sup> und war blassgelb. Dazu kamen 8 cm<sup>3</sup> 10 %ige Lauge. Wegen der ausfallenden Phosphate musste wieder filtriert werden. Das nunmehr grüngelbe Filtrat, in zwei planparallele Flaschen eingefüllt, war der Standard-Vergleichslösung 10 gleich. Urochrom-Uroerythrinwert für 100 cm<sup>3</sup> Harn berechnet =  $\frac{2 \times 21 \times 26 \times 1 \times 10}{20 \quad 18 \quad 2} = 15.1$ , der Urochrom-Uroerythrinwert p.d. = 15.1  $\times 7 = 105.7$ .

2. A. K. 40 J., 38.5°, Pneumonie. Harn-Tagesmenge 800 cm<sup>3</sup>, sauer, spez. Gew. 1022, nitritfrei. Der Harn war stark rot, aber klar. Starke Aldehydreaktion, Diazo normal. 10 cm<sup>3</sup> wurde 4  $\times$ , also auf 40 mit Wasser verdünnt, davon wurden 20 cm<sup>3</sup> mit 1 cm<sup>3</sup> Eisessig und 5 Amylalkohol im Schütteltrichter ausgeschüttelt. Das Talkfiltrat betrug 17 cm<sup>3</sup> und war urobilinfrei. Zu den 17 cm<sup>3</sup> kamen 8 cm<sup>3</sup> 10 %ige Lauge. Das Filtrat = 23 cm<sup>3</sup> ergab einen Wert, der in Doppelflasche noch eine Spur stärker war, als die Vergleichsflüssigkeit 10. Deshalb kamen zu den zu gleichen Teilen in zwei Flaschen gefüllten 23 cm<sup>3</sup> noch je 1 cm<sup>3</sup> H<sub>2</sub>O, wodurch die Farben völlig gleich wurden. Der Urochrom-Uroerythrinwert betrug  $\frac{4 \times 21 \times 25 \times 25 \times 1 \times 10}{20 \quad 17 \quad 23 \quad 2} = 33.5$  und p. d.  $33.5 \times 8 = 268.0$ .

Haben wir ikterische Harne zu untersuchen, so müssen wir das durch die Amylalkohol-Extraktion und die Talkbehandlung nicht völlig zu beseitigende Bilirubin noch durch konc. Salpetersäure zerstören, welche das Urochrom-Uroerythrin nicht angreift. Doch soll die verwendete  $\text{HNO}_3$ -Menge nicht grösser sein als notwendig ist und versucht man es bei schwächerem Bilirubingehalt zunächst mit  $\frac{1}{4}$ — $\frac{1}{2}$  cm<sup>3</sup> Säure.

3. R. S., 23 J., Ikterus kat., totaler Verschluss. Aldehydreaktion negativ, starker Bilirubingehalt. Tagesmenge 1400, neutral, spez. Gew. 1020, nitrisfrei. 10 cm<sup>3</sup> des klaren, stark rotgelben Harns wurden 5mal verdünnt, davon 20 + 1 Eisessig + 5 Amylalkohol ausgeschüttelt. Das Talkfiltrat war noch bilirubingelb. Deshalb wurden die vorhandenen 18 cm<sup>3</sup> mit 1 cm<sup>3</sup> konc.  $\text{HNO}_3$  versetzt und gemischt. Die Gelbfärbung verschwand binnen 20 Minuten bis auf eine Spur. Diese Spur wurde durch nochmaligen Zusatz von Talk vollkommen beseitigt<sup>1</sup>. Das Filtrat = 16 cm<sup>3</sup> musste aber mit mehr Lauge versetzt werden, da ja  $\text{HNO}_3$  dazugekommen war. Dazu waren 16 cm<sup>3</sup> notwendig. Es betrug 30 cm<sup>3</sup> und entsprach in 3 Flaschen hintereinander der Vergleichsflüssigkeit 10. Der Urochrom-Uroerythringehalt war gleich  $\frac{5 \times 21 \times 19 \times 32 \times 1 \times 10}{20 \quad 18 \quad 16 \quad 3} = 36.9$  und p. d.  $36.9 \times 14 = 516.6$ .

Eine besondere Behandlung erfordern Harne mit pos. Diazo-reaktion. Urochromogen färbt sich auch mit Alkali grüngelb. Haben wir normale Harne vor uns, die eine Spur Urochromogen enthalten, so können wir den von der Mitbestimmung dieses Körpers herrührenden Fehler eventuell vernachlässigen. Doch habe ich mich bemüht, die Grösse desselben mit Rücksicht auf pathologische Harne zu bestimmen, indem ich im Ammonsulfat-Filtrat nach Ansäuerung mit Eisessig und Aether-Extraktion (zur Beseitigung der auch eine Diazo-reaktion gebenden Oxyssäuren) den Diazowert und den ihm nach Alkalizusatz entsprechenden Farbwert des Urochromogens bestimmt habe. Zu diesem Zwecke war es aber zuerst notwendig, eine einer schwachen Diazo-reaktion entsprechende Standardlösung herzustellen. Dieselbe hat folgende Zusammensetzung:

Oswald Rot 0.2: 100 H<sub>2</sub>O 10fach verdünnt; davon 25 cm<sup>3</sup> + 30 H<sub>2</sub>O = 55 cm<sup>3</sup>.

Oswald Gelb 0.2: 100 H<sub>2</sub>O 2 cm<sup>3</sup>.

<sup>1</sup> Minimale Spuren von Bilirubin stören die Bestimmung nicht, weil dasselbe durch KOH sich nicht nur nicht in seiner Gelbfärbung vertieft, sondern noch weiter abblässt (Biliverdinbildung).

Volumen am Wasserbad abgedampft. Die erhaltene, abgemessene Flüssigkeit wurde mit Lauge versetzt und der Farbwert bestimmt.

Z. B. Typhusharn, Tagesmenge 600 cm<sup>3</sup>. Diazo- und Urochromogenreaktion stark positiv. Der Diazo-Wert, wurde mit 10.6 pro 100 Harn berechnet (s. fr.). Vom hiezu verwendeten, mit Talk gut ausgeschüttelten Ammonsulfat-Filtrat waren noch 9 cm<sup>3</sup> vorhanden, dazu kamen 27 cm<sup>3</sup> konc. Alkohol. Das stark am Wasserbad eingeeengte Filtrat wurde auf dasselbe Volumen gebracht, wie es dem Harn entsprach,  $\frac{9 \times 25}{33} = 6.8$  cm<sup>3</sup>. Der

Farbwert dieser Flüssigkeit betrug 4 pro 100, nach Zusatz von 3 cm<sup>3</sup> Alkali aber 16.4. Der Farbstoffwert von 4 war durch das an sich etwas gelbliche Urochromogen bewirkt, weshalb der Alkaliwert von 16.4 dem Diazo-Wert von 10.6 gleichgesetzt werden konnte. Es entfiel demnach auf einen Diazo-Wert von 1 ein Alkali-Wert von 1.5.

Dieser Wert, in mehreren Fällen bestimmt, schwankte zwischen 1.5 und 1.6 des gelben Standard-Wertes. Auf Grund dieser Berechnung müsste vom Alkaliwert des Urochrom-Uroerythrins pro 100 Harn, entsprechend dem normalerweise etwa 1 betragenden Diazo-Wert, 1.5 abgezogen werden, was bei negativer Diazoreaktion und einem spez. Gew. von 1020—25 auch ohne gesonderte Bestimmung geschehen kann. In pathologischen Harnen mit positiver Diazo-probe muss aber dieser Wert bestimmt werden. So ergab obiger Typhusfall einen Urochrom-Uroerythrinwert von 40 und p. d. 320. Nach dem Diazo-Wert von 10.6 sind aber von 40 für das Urochromogen abzuziehen  $10.6 \times 1.5 = 15.9$ , so dass für Urochrom-Uroerythrin nur übrigbleibt  $40 - 15.9 = 24.1$  und p. d. 144.6.

### III. Urochrom-Uroerythrinausscheidung des gesunden und kranken Organismus.

Die Tabelle illustriert die Urochrom-Uroerythrinausscheidung des gesunden und kranken Organismus. In ihr ist beim 1. und 22. Fall ausser dem colorimetrischen ein Gewichtswert angegeben. Dieser wurde durch Darstellung von harnsäurefreiem, reinen Uroerythrin resp. Urochrom aus Sedimentum lat. und Wägung nach vorheriger Bestimmung des entsprechenden Farbwertes durch Alkalizusatz gewonnen. Der 100 Einheiten der Standardlösung 10 entsprechende Gewichtswert betrug 70 mg. Ausser den Farbwerten für 100 cm<sup>3</sup> Harn und pro die ist auch der Wert pro Kilo-



Tabelle der Urochrom-Uroerythrinausscheidung

| Name, Alter und Gewicht | Diagnose und Temp.                | Harn pro die, spez. Gew. | Besondere Reaktionen |
|-------------------------|-----------------------------------|--------------------------|----------------------|
| 1. M. W., 63 J., 62 Kg. | Eigen, normal                     | 1300, 1020               | 0                    |
| „ „ „ „ „               | Tagesharn von 9 <sup>h</sup> =    | 300, 1023                | „                    |
| „ „ „ „ „               | Abendh. nach der                  |                          |                      |
| „ „ „ „ „               | Hauptmalzeit von 5 <sup>h</sup> = | 200, 1025                | „                    |
| „ „ „ „ „               | Nachtharn von 10 <sup>h</sup> =   | 800, 1012                | „                    |
| 2. B. A., 10 J., 27 „   | normal                            | 800, 1024                | „                    |
| 3. E. E., 5, 18 „       | „                                 | 800, 1016                | „                    |
| 4. I. L., 57, 79 „      | „                                 | 1500, 1018               | „                    |
| 5. S. A., 76, 55 „      | Senium, 37°                       | 1800, 1012               | „                    |
| 6. G. S., 17, 102 „     | Adipositas, n.                    | 600, 1035                | „                    |
| 7. T. B., 18, 69 „      | Morb. Addison, n.                 | 1400, 1018               | „                    |
| 8. A. L., 24, 110 „     | Akromegalie, n.                   | 1200, 1022               | „                    |
| 9. F. S., 61, 67 „      | Vit. cord. 37.5°                  | 700, 1024                | „                    |
| 10. V. F., 63, 71 „     | Aortitis luica, 37.3°             | 800, 1026                | „                    |
| 11. I. L., 27, 56 „     | Pneumonie, 38.9°                  | 900, 1021                | Urobilin             |
| 12. U. B., 17, 51 „     | Typhus 40.1°                      | 600, 1027                | Diazo pos 4          |
| 13. S. L., 37, 70 „     | Tbc. pulm. 38.2°                  | 1000, 1022               | „ pos 3              |
| 14. K. E., 54, 47 „     | „ „ 37.9°                         | 800, 1025                | 0                    |
| 15. A. A., 79, 49 „     | Ca ventr., n.                     | 800, 1020                | Aldehyd stark        |
| 16. N. B., 73, 45 „     | „ „ 37.8°                         | 1000, 1017               | Diazo pos 2          |
| 17. P. W., 69, 80 „     | Ca hepatis, Ascites, 38.5°        | 600, 1024                | Aldehyd stark        |
| 18. K. E., 42, 58 „     | Cirr. hepatis, Ascites, n.        | 1200, 1016               | „ „                  |
| 19. H. P., 72, 60 „     | Anaemia pern., „                  | 1000, 1021               | 0                    |
| 20. N. H., 74, 45 „     | „ „ „                             | 900, 1024                | Ald. stark           |
| 21. K. R., 55, 81 „     | Neph. chron. 37.2°                | 1200, 1018               | Albumen 6 ‰          |
| 22. A. F. 32, 60 „      | Hepatitis, tot. Verschluss, n.    | 2500, 1012               | Bilirubin            |
| 23. K. I., 17, 64 „     | „ 37.3°                           | 1200, 1023               | Bil. u. Urobilin     |
| 24. A. S., 56, 52 „     | Ca pankr., tot. Verschl. n        | 700, 1024                | Bilirubin            |

wechsel — etwa Gewebszerfall — bewirkten Erhöhung der Farbstoffbildung fehlen bis jetzt direkte Anhaltspunkte. Eher können wir eine Verminderung der Bildung bei erlahmendem Stoffwechsel nachweisen. Es ist jedoch wahrscheinlich, dass unter dem Einfluss gewisser Noxen vermehrte Bildung und Ausscheidung im Harn er-

des gesunden und kranken Organismus.

| Urochrom-Uroerythrin    |                        |            |        | Anmerkung   |
|-------------------------|------------------------|------------|--------|---|
| pro 100 cm <sup>3</sup> | pro die                | pro Stunde | pro Kg |   |
| 8.0                     | 104                    | 4.3        | 1.7    | Ur.-Uroerythrin pro die =<br>72 mg  |
| 13.5                    | 9 <sup>h</sup> = 40.5  | 4.5        | —      |   |
| 13.4                    | 5 <sup>h</sup> = 26.8  | 5.4        | —      |   |
| 4.7                     | 10 <sup>h</sup> = 37.6 | 3.7        | —      |   |
| 8.8                     | 70.4                   | —          | 2.6    |   |
| 7.5                     | 60                     | —          | 3.2    |   |
| 7.5                     | 112.5                  | —          | 1.4    |   |
| 2.5                     | 45                     | —          | 0.8    |   |
| 24                      | 144                    | —          | 1.4    |   |
| 7.5                     | 105                    | —          | 1.5    |   |
| 16                      | 192                    | —          | 1.7    |   |
| 24.5                    | 171.5                  | —          | 2.5    |   |
| 29.6                    | 236.8                  | —          | 3.3    |   |
| 28.6                    | 257.4                  | —          | 4.5    |   |
| 24.1                    | 144.6                  | —          | 2.8    |   |
| 18.2                    | 182                    | —          | 2.6    | Chron. Verlauf<br>gastr. Urobilinurie<br>Kachekt. Urochrom-<br>Uroerythrinverarmung |
| 10.5                    | 84                     | —          | 1.5    |   |
| 13.2                    | 105.6                  | —          | 2.1    |   |
| 5.7                     | 57                     | —          | 1.2    |   |
| 40.8                    | 244.8                  | —          | 3.0    |   |
| 22.2                    | 266.4                  | —          | 4.6    |   |
| 8                       | 80                     | —          | 1.3    |   |
| 9                       | 81                     | —          | 1.8    |   |
| 5.5                     | 66                     | —          | 0.8    |   |
| 20.6                    | 515                    | —          | 8.5    |   |
| 35.8                    | 429.6                  | —          | 6.7    | Ur.-Uroer. p. d. rund =<br>350 mg   |
| 43.6                    | 305.2                  | —          | 5.8    |   |
|                         |                        |            |        | Kach. Ur.-Uroerythrin-<br>Verarmung   |

folgt, welche aber durch die beherrschende Rolle der Leber überdeckt wird, so dass es schwer ist, eine vermehrte Ausscheidung infolge von Mehrangebot an die Leber — wie vielleicht bei manchen fieberhaften Erkrankungen — von einer Mehrausscheidung infolge von Stauung in der Leber zu trennen.

Das Urochrom-Uroerythrin ist ebenso wie das Urobilin und Bilirubin klinisch zumeist ein Stauungszeichen. Die Stauung hat ihren Sitz in der Leber, wenn auch nicht immer Erkrankungen derselben vorliegen. Eine gewisse Blutstauung in ihr ist auch vielfach die Ursache für das vermehrte Auftreten des Farbstoffs bei den fieberhaften Krankheiten, die zunächst das Herz (fieberhafte Tachykardie) und in weiterer Folge die Leber alterieren. Das Gleiche kann von der Lunge aus geschehen.

Die Fülle der pathogenetischen Ursachen für die Entstehung einer Uroerythrinurie ist so gross, dass es nur wenige Krankheiten gibt, welche nicht eine Steigerung derselben bewirken. Dies könnte dem Farbstoff eine gewisse Banalität verleihen, aber in der quantitativen Bestimmung besitzen wir doch eine Differenzierungsmöglichkeit, die von diagnostischem Wert sein kann. In einer anderen Richtung wieder kann die Relation zum Urobilin Verwertung finden. Denn obgleich beide Farbstoffe einen weitgehenden Parallelismus zeigen, ist ihre Ausscheidung doch nicht gleichsinnig. Das Urobilin kann ausser bei Stauungen in der Leber noch aus zwei anderen Gründen vermehrt in den Harn übertreten. Es gibt eine *gastrische Urobilinurie*, welche entsteht, wenn durch einen offenen Pylorus Urobilin in den Magen übertritt, von welchem dasselbe rasch in die Niere gelangt<sup>1</sup>. Dieser gastrischen<sup>2</sup> Urobilinurie braucht keine Vermehrung des Urochrom-Uroerythrins im Harn zu entsprechen. Eine zweite Quelle für vermehrte Urobilinausscheidung kann das vermehrte Angebot bei Hämolysen sein. Hier ist die Resorption des reichlich im Dünndarm zu Gebote stehenden Urobilins die Quelle. Diese Urobilinurie hat also *hämolytischen Ursprung*. Auch in solchen Fällen kann der Urobilinwert hoch, der Urochrom-Uroerythrinwert dagegen normal sein. Doch schliesst weder die gastrische noch die hämolytische Urobilinurie aus, dass eine Leberstauung daneben vorhanden sein kann. Im Gegensatz zur cardio-pulmonalen und hepatalen Stauung scheinen Stauungen im Portalsystem ausserhalb der Leber nur dann vermehrte Farbstoffausscheidung zu bewirken, wenn gleichzeitig eine Lebererkrankung vorhanden ist. Daher weist eine stärkere Ausscheidung bei Ascites in erster Reihe auf die Leber hin, während Ascites ohne Vermehrung des Farbstoffs andere Ursachen zu haben pflegt.

Die Urochrom-Uroerythrinausscheidung kann auch erniedrigt sein. Dies tritt deutlich bei der chron. Nephritis zutage. Eine

<sup>1</sup> Ladage, Diss. Leyden 1899, Ref. Malys Jahresber.

<sup>2</sup> Siehe Meinel. Centr. Bl. f. inn. Med., 1903.

Herabsetzung finden wir ferner oft bei der An. pern. mit oder ohne Urobilinurie. Hier handelt es sich nicht um Retention, sondern um ein herabgesetztes Angebot von Farbstoff an die Leber. Diese verminderte Ausscheidung, die wir auch bei anderen langdauernden Erkrankungen antreffen können, möchte ich als »kachektische Urochrom-Uroerythrin-Verarmung« bezeichnen. Auf verminderte Uroerythrinausscheidung bei kachektischen Ikterusfällen habe ich schon früher<sup>1</sup> hingewiesen.

Die Urochrom-Uroerythrinausscheidung wurde auch bei Störungen der endokrinen Drüsen untersucht. Ein Fall von M. Addison, eine Akromegalie, mehrere Diabetesfälle zeigten normalen, eine hypophysäre Fettsucht einen etwas verminderten Kilogrammwert. Dagegen dürfte Basedow stets zu einer Erhöhung der Ausscheidung Anlass geben.

#### IV. Zur Frage des Ursprungs des Urochrom-Uroerythrins.

Garrod<sup>2</sup> sagt, dass klinische Beobachtungen auf die Leber als Entstehungsort des Uroerythrins hinweisen, Beweise für eine Beziehung zum Blut- oder Gallenfarbstoff liegen aber nicht vor. Drabkin rechnet das Urochrom zu den rein endogenen Stoffwechselprodukten; seine Abstammung vom Hämoglobin sei nicht unmöglich, wenn auch aus eigentlichem Zelleiweiss wahrscheinlicher (Myohämoglobin, Keilins Cytochrom oder Warburgs Atmungsferment). Heilmeyer weist darauf hin, dass das Uroerythrin bei Leberkrankheiten vermehrt ausgeschieden wird. Er kommt bezüglich des Urochroms fast genau zu den gleichen Ergebnissen wie bezüglich des Uroerythrins. Im Lichte meiner Untersuchungen bieten diese Ergebnisse nichts Ueberraschendes, doch haben die von ihm betonten Beziehungen beider Farbstoffe zum Blutzerfall<sup>3</sup> etwas Gezwungenes an sich; weder Dombrowski<sup>4</sup> noch Hohlweg<sup>5</sup> konnten aus Urochrom Hämopyrrol darstellen.

Dass der in Krankheiten vermehrt ausgeschiedene Farbstoff nicht schlechtweg das Ergebnis eines pathologischen Stoffwechsels

<sup>1</sup> Diagnose und Prognose aus dem Harn, S. 108, Verlag f. Medizin, Hans Huber, Bern.

<sup>2</sup> Journ. of Phys. Bd. 17, 1894/95.

<sup>3</sup> Med. Spektrophotometrie, S. 216 u. 231.

<sup>4</sup> Zeitschr. f. Phys. Chem., Bd. 54, 390, 1908.

<sup>5</sup> Bioch. Zeitschr., Bd. 13, 199, 1908.

ist, beweist die leichte Steigerung seiner Ausscheidung bei mechanischen Behinderungen der Gallenabsonderung. Hier liegen ähnliche Verhältnisse wie beim Urobilin vor, aus dessen vom Darm zur Leber gehenden Strom unter den gleichen Bedingungen bedeutende Mengen paracholisch gegen die Niere abgedrängt werden können. Sowie aber dieses Urobilin auf eine stärkere Quelle hinweist, so werfen auch die im Harn auftretenden erhöhten Urochrom-Uroerythrinquantitäten ein Licht auf einen Stoffwechsel, dessen Umfang wir nach den physiologischen Werten nicht zu beurteilen im Stande wären. Während wir aber beim Urobilin Beziehungen zur Hämolyse kennen, sind uns beim Urochrom-Uroerythrin Beziehungen zu einem besonderen Stoffwechselvorgang bisher unbekannt.

Versucht man etwas Sicheres über den Ursprung dieses Farbstoffs auszusagen, so erkennt man bald, dass wir hier noch völlig auf Vermutungen angewiesen sind. An welche der beiden Modifikationen sollen wir uns halten, wenn wir nach Analogien im Körper suchen? Infolge der alkalischen Reaktion in den Geweben ist es eher berechtigt, die gelbe Alkali-Modifikation des Urochroms als die rötliche des Uroerythrins unseren Vorstellungen zu Grunde zu legen. Suchen wir nach ähnlich gefärbten Geweben oder Flüssigkeiten, so stossen wir zunächst auf die Lipochrome. Wir wissen aber, dass diese Stoffe exogenen Ursprungs sind. Beim Diabetes, wo die Lipochrome im Blut vermehrt sind, ist eine Steigerung nicht festzustellen.

Drabkin konnte durch Beigabe von Chlorophyll oder Hb zur farblosen Grunddiät beim Hunde keine Änderung der Harnfarbe erzeugen, dagegen ergaben Adrenalin, Thyroxin und Phlorrhizin, also den Stoffwechsel steigernde Substanzen, bedeutende Erhöhungen, die Entfernung der Schilddrüse hinwiederum starke Verminderung der Ausscheidung. *Die Kurve der Urochrom-Uroerythrinausscheidung zeigt beim Menschen von der Kindheit bis in das Senium einen stetigen Abfall.* Beziehungen zur Intensität des Zellebens sind nach Drabkin nicht zu verkennen. Beim Myxoedem und bei schwereren Formen des Parkinsonismus habe ich selbst starke Verminderungen der Urochrom-Ausscheidung festgestellt.

Zwei Tatsachen könnten uns dem Ursprung des Farbstoffs näher bringen. Die eine ist die enge Verbundenheit desselben mit der Harnsäure. Im Sed. lat. ist der Farbstoff so innig mit der Harnsäure verbunden, dass man ihn aus dieser Verbindung schwer tren-

nen kann. Es wäre daher möglich, dass der Zerfall der Kern- und anderer Nukleoproteine, aus welchen die endogene Harnsäure entsteht, auch die Quelle des Farbstoffs ist, *dass er also aus einer in den Zellen vorhandenen gefärbten Verbindung stammt*. Diesen Farbstoff bekommen wir nicht zu Gesicht, weil wir fast nie reine Zellen in genügend grosser Menge antreffen. Dort wo dies aber der Fall ist, wie beim Eiter, können wir Gelbfärbung feststellen; sie ist nicht an die Flüssigkeit des Eiters, sondern seine festen Bestandteile, die kernreichen Leukozyten, geknüpft. Das Chlorom, eine besondere Form des Lymphosarkoms, zeigt eine Färbung, von der Recklinghausen und ebenso Sternberg<sup>1</sup> meinen, dass es sich nicht um Lipochrom, sondern »um eine Parenchym-Farbe handelt, welche der gelbgrünen Farbe des Eiters vergleichbar ist«.

— Einige Eiterproben wurden von mir daraufhin untersucht, ob sich ein dem Urochrom-Uroerythrin ähnlicher Farbstoff aus Eiter gewinnen lässt. Nach Ausschaltung der Fehlerquelle, die von beigemengtem Blutfarbstoff herrühren konnte (durch spektroskopische Untersuchung), wurde festgestellt, dass an sich gelbe Eiterextrakte sich durch Alkali stärker gelb färben und auf Zusatz von konz.  $H_2SO_4$  Rotfärbung geben. Damit war die Anwesenheit eines dem Urochrom-Uroerythrin ähnlichen Farbstoffs im Eiter wahrscheinlich gemacht; seine Quantität dürfte nicht in allen Zellen gleich sein, denn blutfreie Muskelextrakte gaben z. B. keine deutliche Gelbfärbung mit Alkali.

Die mit ungefähr 350 mg veranschlagte normale Urochrom-Uroerythrinbildung p. d. stellt für ein endogenes Produkt einen ziemlich hohen Wert vor. Es muss sich daher um ein relativ grosses Gewebe handeln, aus dem der uns hier beschäftigende Farbstoff entsteht. Kann die Masse der Körperzellen, wobei vielleicht die Kerne die hauptsächlichsten Träger des Farbstoffs sind, dieser Vorstellung entsprechen? Ich glaube ja. Vergleichen wir die Menge der im Harn p. d. ausgeschiedenen endogenen Harnsäure, welche normalerweise 3—400 mg beträgt<sup>2</sup>, mit der von mir auf 350 mg geschätzten normalen Urochrom-Uroerythrinbildung, so könnten diese Mengen einander entsprechen. Schwieriger ist es sich vorzustellen, dass der doch vielfach mit vermehrtem Kernzerfall einhergehende pathologische Stoffwechsel nicht auch irgendwie in den Werten zum

<sup>1</sup> Handbuch, d. spez. path. Anatomie, I. Springer, 1926.

<sup>2</sup> Bodansky, Introduction to Phys. Chem., S. 442.

Ausdruck kommen sollte. Aber hierüber wissen wir nichts Sicheres, da ausser bei der Hepatitis und Tumoren mit totalem Gallenwegsverschluss uns niemals die ganze im Stoffwechsel gebildete Menge des Farbstoffs zu Gesichte kommt.

### Zusammenfassung.

1) Der normale gelbe Harnfarbstoff Urochrom ist durch die alkalischen Valenzen des Harns mit gelber Farbe gelöstes Uroerythrin.

2) Beide Farbstoffe können durch colorimetrischen Vergleich mit den gleichen künstlichen Farbmischungen quantitativ bestimmt werden.

3) Die stärkste Urochrom-Uroerythrinausscheidung wird bei totalem Gallenwegsverschluss im Beginne der Erkrankung beobachtet. Sie beträgt hier rund 350 mg p. d., während normalerweise nur etwa 70 mg durch den Harn ausgeschieden werden.

4) Die Menge von 350 mg dürfte auch die im normalen Stoffwechsel eines Erwachsenen gebildete Quantität sein, von der physiologisch der grösste Teil durch die Leber abgebaut wird.

5) Das Urochrom-Uroerythrin gehört zu den Stauungszeichen des Harns. Je grösser die durch die verschiedensten Ursachen auslösbare Behinderung der Lebercirculationen ist, umso mehr nähert sich der im Harn aufscheinende Wert dem bisher festgestellten Maximum von 350 mg.

6) Die Urochrom-Uroerythrinausscheidung ist bei schweren Nierenschädigungen (Schrumpfniere), ebenso aber auch bei kachektischen Zuständen der verschiedensten Art und im Senium vermindert.

7) Es wird hypothetisch die Abstammung des Urochrom-Uroerythrins aus einem in den Zellen bzw. Zellkernen enthaltenen Farbstoff erörtert und die bei den Eiterkörperchen sichtbar in Erscheinung tretende Gelbfärbung damit in Zusammenhang gebracht.

### Conclusions.

1. The normal yellow urine pigment Urochrom is Uroerythrin dissolved with yellow colour by the alkaline urine-valencies.

2. Urochrom and Uroerythrin can be determined by colorimetric comparison with the same artificial colour-mixtures.

3. The greatest Urochrom-Uroerythrin output is observed in total occlusion of the gallways in the beginning of the disease. It amounts here round 350 mg p. d., while normally only about 70 mg are excreted by the urine.

4. The amount of 350 mg seems to be the quantity formed in the normal chemistry of the body, but physiologically is the greatest part destroyed by the liver.

5. Urochrom-Uroerythrin belongs to the signs of stase in urine. The greater the differently caused obstacles for liver-circulation are, the nearer comes the output in urine to this hitherto found maximum of 350 mg p. d.

6. The Urochrom-Uroerythrin output is diminished in heavy kidney diseases (shrink-kidney), likewise also in various kachectic conditions and in the senium.

7. Hypothetically is discussed the origin of Urochrom-Uroerythrin from a colouring matter in the cell resp. in the cell-nucleus and the visible yellow colour of the pus-cells is brought in connection with it.

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From Drammen Hospital, Medical Dept. Norway. (Chief: Dr. med. O. Römcke) and Röntgen Dept. (Chief: Dr. P. Natvig).

## Results of Medical Treatment of Gastric and Duodenal Ulcer.

(A Clinical-röntgenological Re-examination of 382 Patients).<sup>1</sup>

By

P. NATVIG, O. RÖMCKE and O. SVAAR-SELJESÆTER.

(Submitted for publication October 30, 1942.)

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The treatment of chronic gastric and duodenal ulcers during the last twenty-five years has varied from medical to surgical and back again. Hitherto it has nowhere been found possible to draw up the final lines of procedure for the treatment, nor can we expect to be able to do so as long as the etiology of the disease is unknown. Moreover, the course to be followed in each particular case is dependent not only on medical but also on social factors. The therapeutic results attained are therefore not commensurable.

The medical mode of treatment follows, generally speaking, the same principles as were laid down by Cruveilhier about 100 years ago. These principles were based, first and foremost, on the observation that gastric ulcer was a curable disorder and, next, that the dietetic and hygienic measures were of importance for the attainment of a cure.

We shall not here go into all the variations of the »ulcer cure» that have been adopted in the course of years. As pointed out by H. G. Dedichen in 1933, the therapy is still based upon clinical experience.

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<sup>1</sup> Paper read in the Norwegian Medical Society on 25/3 1942.

Such new procedures as have been introduced in the ulcer treatment can hardly be shown to have led to improved results.

The treatment we have adopted is the usual cream-milk cure extending over four weeks, with a prolongation of 14 days in particular cases. The diet is at first very scanty and is gradually increased during the course of the cure. Alkalies and warm compresses are employed only in some individual instances. The patients are strictly confined to bed, and in the great majority of cases the conditions in the stomach are ascertained by X-ray examination both before and after the course of treatment. On being discharged the patients are usually enjoined to keep quiet for at least a fortnight and to observe a careful diet for half a year afterwards. Three years after completion of the cure the patients are systematically called up for clinical and röntgenological control-examination. The results of this examination will be set forth in the following pages. So far as we have been able to find, there have not hitherto been published the results of both clinical and röntgenological control-examination of any rather large body of material.

We have confined ourselves to so short an observation period as three years because Åge Nielsen's investigations have shown that 90 per cent of the recurrences appear within  $2\frac{1}{2}$  years after the treatment. If the patient has had no recurrence in these years, he should therefore have a good chance of continued freedom from symptoms. Meanwhile, our further investigations show that a good many recurrences arise after 3 years, and we hope to be able to revert to this matter on a future occasion.

Before proceeding to speak of our results we shall, however, try to illustrate the importance of this disorder by means of some figures. During  $6\frac{1}{2}$  years (from 1/1—35 to 30/6—11) the number of patients treated in the Medical Unit of the hospital was 10,580, of whom 904 were suffering from gastric or duodenal ulcer. To these may be added 150 re-admissions. Ulcers of the stomach and duodenum thus constitute 10 per cent of the total number of cases treated. From this it will be understood why we have deemed it imperatively necessary to attempt, at any rate as far as we are concerned, to draw up some few guiding lines for our therapy.

The follow-up investigation concerns the first 3-year period after leaving the hospital and includes 382 patients, of whom 152 had suffered from gastric and 230 from duodenal ulcer, in all cases

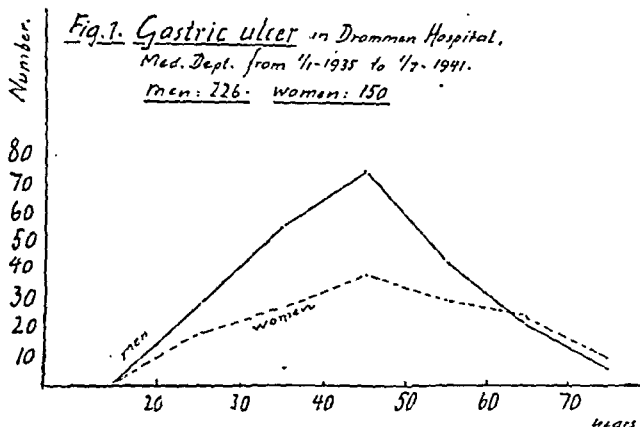
verified by X-ray examination. The age-classification for the two groups was as follows:

Table I.  
Distribution according to age.

|                      | < 20 | 21—30 | 31—40 | 41—50 | 51—60 | 61—70 | > 70 |
|----------------------|------|-------|-------|-------|-------|-------|------|
| Gastric ulcer .....  | 1    | 28    | 35    | 40    | 38    | 6     | 4    |
| Duodenal ulcer ..... | 15   | 56    | 80    | 38    | 33    | 7     | 1    |

Of patients with gastric ulcer 81 were men and 71 women, of those with duodenal ulcer 170 were men and 60 women.

We here find repeated the usual experience that duodenal ulcer occurs far more frequently in men than in women, while the fre-



quency of gastric ulcer is more or less the same in both sexes. Further it would seem that *ulcus duodeni* occurs at an earlier age than gastric ulcer. In order to check these figures we have prepared a statistical table of the ages of ulcer patients in the period from 1/1—35 to 1/7—41. Only those treated for the first time are included and the material includes 904 cases, whereof 376 with gastric ulcer and 528 with duodenal ulcer. (Fig. 1 and Fig. 2.)

In this larger body of material we find again more or less the same conditions, but here there is a distinct preponderance of males also among the patients with gastric ulcer. Further it is seen that the tendency towards greater frequency of duodenal ulcer in the lower age-groups is found only among men. The curve for duodenal ulcer here reaches the maximum between the ages of 30 and 40, while

Fig. 2. Duodenal ulcer  
in Drammen Hospital, Med. Dept.  
from 1/1-1935 to 1/7-1941.  
men: 405. women: 123.

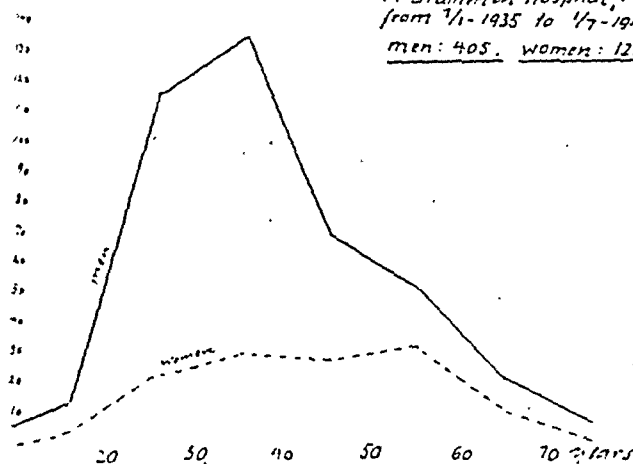


Fig. 3. Duodenal- and gastric ulcer in men  
percentage according to age

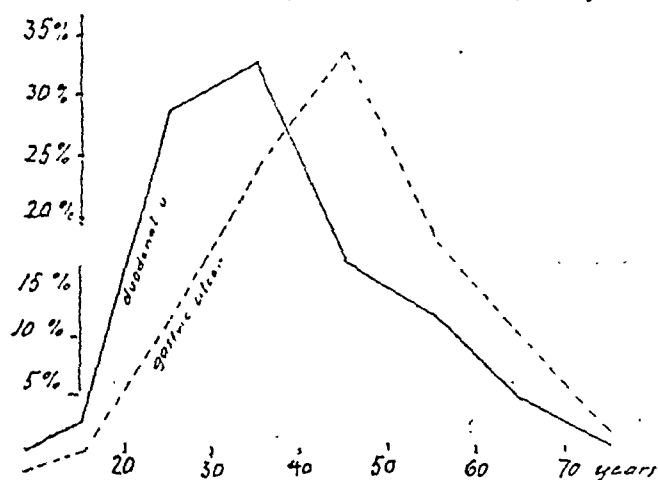
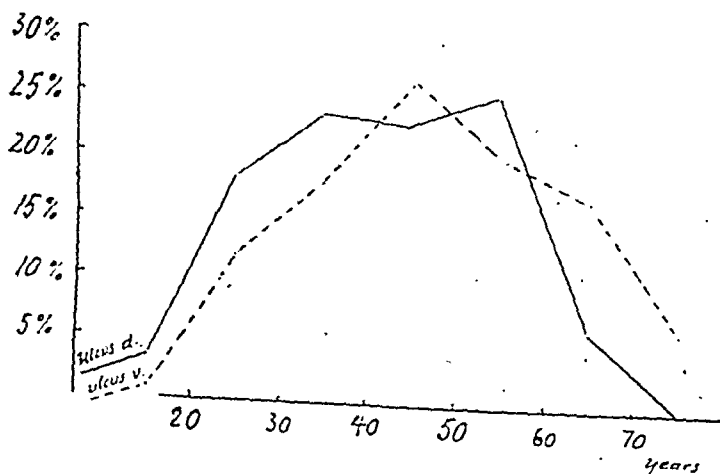


Fig. 4. Duodenal- and gastric ulcer in women  
percentage according to age.



gastric ulcer shows the greatest frequency at the age between 40 and 50. (Fig. 3.)

Among the women (Fig. 4) the age-curves for gastric and for duodenal ulcer practically coincide.

This difference in frequency according to age is of considerable importance for the therapy, especially as regards the question of operative treatment, where the age of the patient may be the decisive factor in the choice of therapeutic procedure.

### *Duration of the illness before admission.*

It will obviously always be difficult to give exact particulars as to the duration of the malady on the basis of the clinical observations alone. We are therefore obliged to content ourselves with approximate figures. On the basis of the anamnestic data the material has been divided into the following groups:

Table II.

| Duration of illness | Gastric ulcer | Duodenal ulcer |
|---------------------|---------------|----------------|
| Under 1 year .....  | 43            | 62             |
| 2—5 years .....     | 51            | 72             |
| 6—10 years .....    | 23            | 42             |
| 11—20 years .....   | 25            | 41             |
| Over 20 years ..... | 10            | 13             |

On setting up these figures in a graph (Fig. 5) it will be found that the curves for gastric and for duodenal ulcer run practically speaking parallel. From this point of view the two groups should therefore be commensurable.

### *Clinical follow-up examination.*

Only for four patients is the subsequent history of the case unknown. As to the remainder we find that 67 of the 152 patients with gastric ulcer are free from symptoms during three years and 79 of the 230 patients with duodenal ulcer. In other words, over 44 per cent of the patients in the first group and 34 per cent of those in the

Fig. 5. Duration of illness  
before diet-cure.



second group present no clinical symptoms in the three-year period. Before proceeding to deal more fully with the results of the subsequent examination it is necessary to define more precisely what we have designated freedom from symptoms. In order to be assigned to that group the patient must have been living on ordinary diet without showing signs of dyspepsia. Meanwhile, there will always be found some patients whose classification is a matter of doubt. Thus some may for a very short period been troubled by indefinite abdominal symptoms, which have caused them to take dietetic precautions during that time. These have nevertheless been included in the symptomfree group. To the dyspepsia group are assigned, on the other hand, all patients who have had to pay special attention to diet during a long period in order to avoid dyspeptic troubles. In separate groups are entered patients who have had manifest hemorrhage or perforating ulcer. As already mentioned, four patients failed to present themselves for re-examination and one patient afterwards died of cancer recti.

The material is divided into groups according to the duration of the symptoms (Tables III and IV — Figs. 6 and 7).

Table III.  
*Gastric ulcer.*

Duration of symptoms:

|                |                   |    |    |     |
|----------------|-------------------|----|----|-----|
| Under 1 year:  | { Symptomfree     | 26 | 43 | 152 |
|                | { Dyspepsia       | 12 |    |     |
|                | { Hemorrhage      | 2  |    |     |
|                | { Not re-examined | 3  |    |     |
| 2— 5 years     | { Symptomfree     | 26 | 51 |     |
|                | { Dyspepsia       | 25 |    |     |
| 6—10 years:    | { Symptomfree     | 6  | 23 |     |
|                | { Dyspepsia       | 15 |    |     |
|                | { Hemorrhage      | 2  |    |     |
| 11—20 years:   | { Symptomfree     | 5  | 25 |     |
|                | { Dyspepsia       | 18 |    |     |
|                | { Hemorrhage      | 1  |    |     |
|                | { Not re-examined | 1  |    |     |
| Over 20 years: | { Symptomfree     | 4  | 10 |     |
|                | { Dyspepsia       | 6  |    |     |

67 symptomfree out of 152.

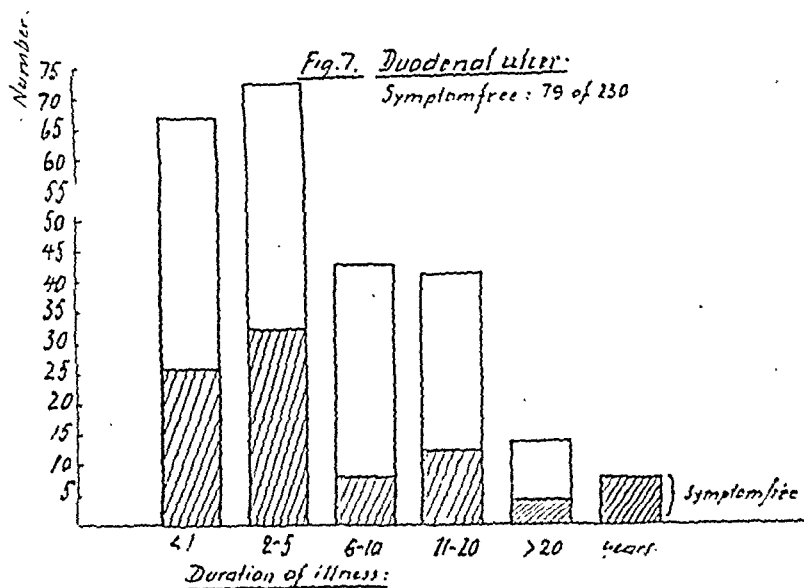
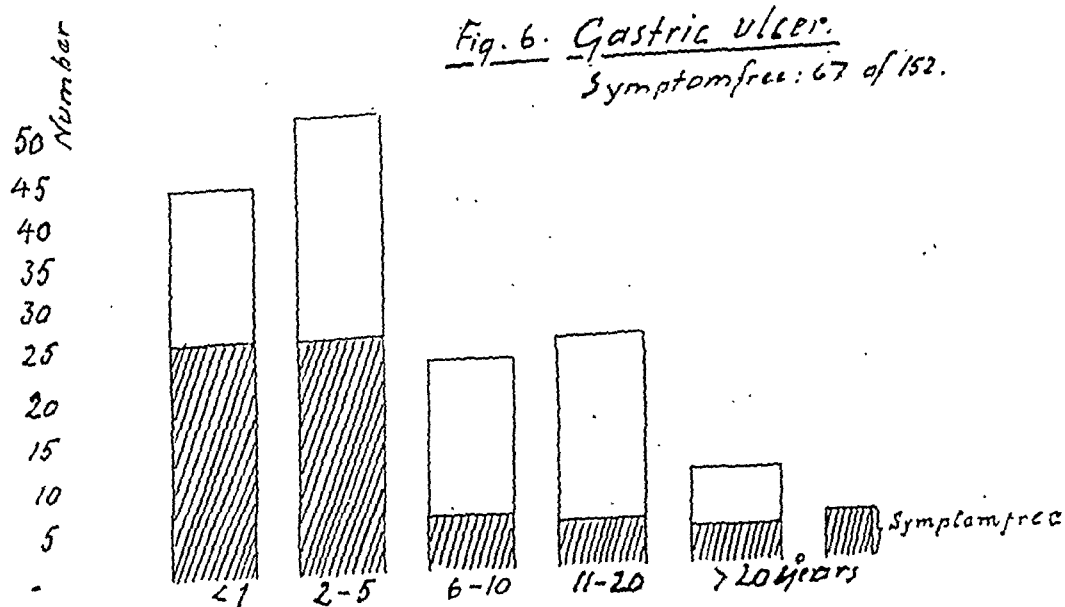
Table IV.  
*Duodenal ulcer.*

Duration of symptoms:

|                |                   |    |    |     |
|----------------|-------------------|----|----|-----|
| Under 1 year:  | Symptomfree       | 23 | 62 | 230 |
|                | Dyspepsia         | 25 |    |     |
|                | Hemorrhage        | 11 |    |     |
|                | Perforating ulcer | 2  |    |     |
|                | + Cancer recti    | 1  |    |     |
| 2— 5 years:    | Symptomfree       | 32 | 72 |     |
|                | Dyspepsia         | 34 |    |     |
|                | Hemorrhage        | 5  |    |     |
|                | Perforating ulcer | 1  |    |     |
| 6—10 years:    | Symptomfree       | 8  | 42 |     |
|                | Dyspepsia         | 30 |    |     |
|                | Hemorrhage        | 4  |    |     |
| 11—20 years:   | Symptomfree       | 12 | 41 |     |
|                | Dyspepsia         | 25 |    |     |
|                | Hemorrhage        | 3  |    |     |
|                | Perforating ulcer | 1  |    |     |
| Over 20 years: | Symptomfree       | 4  | 13 |     |
|                | Dyspepsia         | 9  |    |     |

79 symptomfree out of 230.

Here will at once be noted again the previously known phenomenon that the shorter the history of the illness is, the greater will be.



the number of patients free from symptoms after the cure (Figs. 6 and 7). This applies especially to the first two groups, which comprise patients who had had the malady for less than 1 year or for 2—5 years respectively before treatment. Among these patients over 50 per cent of those with gastric and about 40 per cent of those with duodenal ulcer were free from symptoms in the three-year period. For patients with a longer history of the disease the results are, however, considerably less satisfactory, the number of those free from symptoms being reduced to about the half. For instance,



of patients who had shown signs of the disease for more than 5 years only 25 per cent can expect to be free from symptoms after the treatment. This applies both to patient with gastric and to those with duodenal ulcer. The recurrences consisted chiefly in the reappearance of the dyspeptic troubles. Among the patients with gastric ulcer only 3 per cent presented symptoms of manifest hemorrhage, while such symptoms appeared in 10 per cent of those with duodenal ulcer. Perforation occurred in none of the patients with gastric ulcer, whereas this complication arose in 4 cases of duodenal ulcer.

For pyloric ulcer, which in this material is assigned to the gastric ulcers, the frequency of recurrence is the same as for the combined material — 2—3rds of the patients (14 out of 20) having had relapses after 3 years.

In order to ascertain whether any indications as to the further course of the disease could be obtained already during the treatment every divergency from the regular course was noted in the journals. Of the total number of patients 55 had dyspeptic troubles during the cure. Twelve of these were free from symptoms in the 3-year period, while 43 had had relapses. Thus the frequency of recurrence seem to be somewhat greater within this group than for the rest of the material investigated. The difference, however, is not so great that it can be assigned any special importance. Finally, 73 of the patients with relapses were subjected to operation, — 47 for duodenal and 26 for gastric ulcer, while 56 had a renewed course of dietary treatment — 30 for duodenal ulcer and 26 for gastric.

We have already mentioned that the choice of the mode of treatment is not solely dependent upon medical considerations, but that social factors also come into play. In order to get an insight into this question the material has been divided into two groups, one of which embraces patients with relatively heavy work, while the second group comprises all other occupations.

Of 126 patients with duodenal ulcer who had manual labour 43 were free from symptoms, while of 104 such patients with »other work» 33 were symptomfree. In other words, about one-third in each group.

Of patients with gastric ulcer 29 out of 63 who had manual work and 34 out of 89 who had »other work» were free from symptoms. Thus as regards gastric ulcers patients with labour actually seem to be more favourably situated than the others. Meanwhile, the group

»other work» here chiefly comprises women, so that the two categories are hardly comparable.

In the combined material we find that 72 out of 189 patients with manual work are free from symptoms, while 67 are free from symptoms among 193 patients with »other work». In this investigation it therefore seems to have had no significance as to the result of the treatment whether the patient has had bodily labour or not.

Finally, we have tried to get an insight into the result of the treatment in cases of relapse. Out of 81 patients (35 with gastric and 46 with duodenal ulcer) who have gone through two cures 24 were free from symptoms after the second course of treatment, *i. e.*, about 30 per cent. The result is, as might be expected, somewhat less satisfactory than after treatment for the first time.

On summing up the results of the clinical re-examination we find them to be as follows:

Of patients with gastric ulcer 44 per cent and of patients with duodenal ulcer 34 per cent were subjectively free from symptoms in the three-year period which the inquiry embraced. Where the disease had been present for less than five years before treatment fully half of the patients with gastric ulcer were found to be free from symptoms and about 40 per cent of those with duodenal ulcer. Of patients with a history of illness exceeding five years only one-fourth can expect to get rid of their troubles.

### Röntgenological Investigations.

Some of the patients were subjected to X-ray examination only at the beginning of the diet-cure, but not at the conclusion of the treatment, or at the control examination after three years. Therefore the number of patients in the following tables will be somewhat less than the total number investigated.

Patients admitted to the hospital on account of hemorrhage were not examined by X-rays before the treatment. If no ulcer, or deformity due to ulcer, was found after treatment, the patient in question has not been included in this material (nor in the clinical), in order to exclude patients with hemorrhage due to other causes than ulcer.

At the control examination after three years 329 patients were X-rayed. 156 of these (44.3 per cent) had no niche. (Out of 382 patients 146 (38.4 per cent) were clinically symptomfree.) (Table V).

Among the *gastric ulcers* 58 showed a niche, while in 61 cases no niche was found. Of the 58 patients with niche 51 had had dyspeptic troubles during the three-year period. Of 22 patients with large gastric ulcer who showed no niche on control examination 19 had been free from symptoms. For so far there is good concordance between the subjective condition in the three-year period and the X-ray examination, whereas there is great disaccordance in the group with small gastric ulcers where no niche was found on control examination. Half of the members of this group (21 patients) were found to have had symptoms. The divergency is so great that it can hardly be ascribed to a fault in the X-ray examination, but must be assumed to be due to some factor in the disease itself.

Table V.

*Relation between results of X-ray examination and clinical examination.*

|                      | Findings on X-ray examination after three years | State of patients during 3-year period |
|----------------------|---|--|
| Large gastric ulcer: | { Ulcer present 14                              | { Symptomfree: 4.<br>Dyspepsia: 10.    |
|                      | { Ulcer absent 22                               | { Symptomfree: 19.<br>Dyspepsia: 3.    |
| Small gastric ulcer: | { Ulcer present 44                              | { Symptomfree: 3.<br>Dyspepsia: 41.    |
|                      | { Ulcer absent 42                               | { Symptomfree: 21.<br>Dyspepsia: 21.   |
| Duodenal ulcer:      | { Ulcer present 115                             | { Symptomfree: 11.<br>Dyspepsia: 104.  |
|                      | { Ulcer absent 92                               | { Symptomfree: 47.<br>Dyspepsia: 45.   |

Total number of patients without ulcer on control examination after three years: 156 (44.3 per cent) of 329 examined.

As regards *duodenal ulcers* the findings were as follows:

Of 207 patients 115 (55 ½ per cent) had a niche and 11 of these were free from symptoms, of 92 patients without niche at the examination after three years 45 had had dyspepsia in the three-year period. In this last group we find the greatest discordance between the result of the X-ray examination and the clinical findings, just as in the corresponding group with small gastric ulcers. Several of the patients in these groups must be assumed to have had ulcer for some time in the three-year period, but have been well at the time

of making the control examination. In other cases it might have been difficult to say whether the ulcer had healed or not, as the decision in many instances is a matter of opinion. Finally, it is certain that some of the patients have had dyspepsia without any ulcer being actually present. This fact should be borne in mind when forming a judgment respecting dyspeptic patients with negative X-ray findings.

The reverse situation is well-known, but is not of very frequent occurrence: Some patients may have a niche but no dyspepsia, although dyspepsia will probably make its appearance sooner or later.

### *Importance of the size of the gastric ulcers.*

We observe the well-known circumstance that patients with large gastric ulcers have far better prospects of becoming free from symptoms than those who have small gastric ulcers. An ulcer is reckoned to be large when its diameter exceeds 1 cm.

#### *Free from symptoms in the three-year period.*

38 large gastric ulcers: 60 per cent (23 patients).  
97 small gastric ulcers: 31 per cent (30 patients).

Relatively more of the large than of the small gastric ulcers have lasted for a shorter time than 5 years (with consequent better prognosis), but this fact does not reduce the difference so very much. Of 56 small ulcers which had existed for less than five years 36 per cent (20 patients) gave no symptoms, as against 60 per cent for all the large gastric ulcers.

### *Is it of importance that the ulcer has healed up at the conclusion of the treatment?*

In 344 cases X-ray examination was made for control after conclusion of the diet-cure. The results of this examination were:

|           | Ulcer after cure | Symptomfree in 3-year period |
|-----------|------------------|------------------------------|
| Stomach:  | 50 pos.          | 20 (40 per cent).            |
| "         | 77 neg.          | 28 (36 per cent).            |
| Duodenum: | 89 pos.          | 20 (22 ½ per cent).          |
| "         | 128 neg.         | 46 (36 per cent).            |

The table shows: Of the gastric ulcer patients who had a niche at the conclusion of the treatment 40 per cent are permanently free from symptoms, while 36 per cent are symptomfree among the patients whose ulcer was healed up at the conclusion of the cure. The corresponding figures for duodenal ulcers are 22 ½ per cent and 36 per cent. Thus it seems to have no significance as to the final result whether the gastric ulcer has healed or not at the end of the cure, whereas in the duodenal group the healing up of the ulcer appears to have an advantageous influence. The preponderance of symptom-free patients in the latter group, however, is not so great that any decisive importance can be assigned to the matter.

### *Significance of bulbar deformity.*

We have investigated the question whether deformity of the bulbus due to ulcer has any importance for the result of the dietary treatment. Bulbar deformity may have various causes, such as inflammatory swelling of the mucous membrane, spasms and cicatricial changes. It might be supposed that a large deformity would render difficult the re-establishment of normal functions, and it might perhaps also be regarded as evidence of greater activity of the ulcer.

We have divided the cases of duodenal ulcer into three groups according to the degree of the deformity: slight, medium or severe. The distinction between the groups is not very sharply defined, but between the first and the third group at any rate there is a considerable difference in deformity.

|                                     | No symptoms in<br>3-year period | Dyspepsia |
|-------------------------------------|---------------------------------|-----------|
| Slight deformity of bulbus: 77 pat. | 21 (27 %)                       | 56        |
| Medium " " " 82 pat.                | 28 (34 %)                       | 54        |
| Severe " " " 69 pat.                | 18 (26 %)                       | 51        |

Groups 1 and 3 have respectively 27 and 26 per cent free from symptoms. Therefore no clinical prognostic conclusions whatsoever can be drawn from the degree of deformity.

The results of the röntgenological re-examination are, in brief, the following:

Where ulcer was found on röntgenological control examination 90 per cent of the patients have had dyspepsia, while 10 per cent had a niche without presenting clinical symptoms. Of the patients with small gastric or duodenal ulcers in whom no niche was found at the control examination after three years 50 per cent had had dyspepsia in the three-year period.

The chances of becoming free from symptoms after the diet-cure are twice as great for patients with large as for those with small gastric ulcers.

The degree of bulbar deformity is without significance as regards the prospects of becoming free from symptoms.

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### **What guiding lines for our therapy are we now entitled to draw up on the basis of these investigations?**

In ulcer cases as in other diseases it is important that the patient shall come under treatment as soon as possible. Thus, if the patient is subjected to treatment within the first five years the chances of a good result of the diet-cure will be twice as great as they would be later on. Therefore it seems to us beyond doubt that patients who have got ulcer for the first time ought to go through a regular course of dietary treatment. The question becomes more difficult in case of recurrence. Shall the patient then submit to an operation? With respect to this question our investigations unfortunately supply no definite answer, as our material of recurrence curves is still too small. Meanwhile, the question is in most cases solved by the patients themselves, since most of them wish to try another diet-cure before submitting themselves to operative treatment.

As to whether the dietary treatment ought to be carried out in the hospital or elsewhere our investigations afford no information, as we have no serviceable basis for comparison.

If the patient is free from symptoms after a moderate change of diet, the question of operative treatment will hardly arise. In this matter, however, many extraneous considerations will always come into play. For instance, the nature of the patient's work and his economic situation may in many cases be factors of decisive importance.

As regards the ulcer malady in itself the previous duration of the illness will, as already mentioned, be a factor of great importance for our choice of a mode of procedure. If the patient comes late under dietary treatment the chances of his being cured are so small that operation is more readily advised. In case of duodenal and small gastric ulcers it seems to us reasonable to recommend an operation if the patient gets a relapse after having gone through a regular diet-cure and is not free from symptoms in spite of dietary precautions. In case of large gastric ulcers, where the dietary treatment gives its best results and an operation involves the greatest risk, one ought in our opinion to be more reserved. In this connection, however, we must mention the danger of error in the diagnosis from cancer the is always possible in case of large gastric niches (exceeding 2.5 cm.).

In favour of operative treatment of duodenal ulcer speak also the relatively great risk of renewed hemorrhage (10 per cent after the diet-cure) and the greater possibility of perforation. Hereto may be added that the duodenal ulcer usually occurs at a younger age, when the mortality from the operation is far less than later in life. Moreover, duodenal ulcer is in much higher degree than gastric ulcer a disease of men. Owing to their occupations outside of the home men will as a rule have more difficulty in taking dietetic precautions than women, a circumstance which also weighs strongly in favour of early operative treatment. Meanwhile it must always be borne in mind that an operation is a severe form of treatment, even though the final results of the large resections now usual are in the great majority of cases satisfactory.

Our treatment of ulcer is unfortunately at present no ideal for of therapy, nor will it be so as long as we do not know the etiology of the disease. We have therefore tried to draw up some lines of procedure on the basis of our present experiences. It is to be hoped that the future will provide us with means for curing this disease in a more rational manner.

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(From the Department of Biochemistry, University of Copenhagen. Chief: Professor, Dr. phil. Rich. Ege).

## A Modification of Thordarson's Method for the quantitative determination of Prothrombin in Plasma.

(A simpler mode of preparing the fibrinogen). \*

By

OSKAR THORDARSON, HOLGER BEGTRUP and  
P. FROM HANSEN.

(Submitted for publication December 23, 1942).

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Of the methods available for the determination of the prothrombin content of plasma the methods described by Warner, Brinkhous and Smith (5, 2) and by Thordarson (3, 4) stand out because they allow the determination of comparatively small amounts of prothrombin. This is done by determining the coagulation time of a fibrinogen solution which contains thrombokinase and calcium, after the addition of diluted plasma. By diluting the plasma, the prothrombin content of which is to be determined, its fibrinogen content is at the same time diluted to such an extent, that it can no longer serve as a substrate for the thrombin formed. A solution of fibrinogen obtained by salting out ox plasma with a saturated solution of ammoniumsulphate is therefore used as a substrate. Salting out the fibrinogen is both time-consuming and difficult, and the fibrinogen obtained only keeps for about two weeks. For these reasons the above methods are not suitable for ordinary routine work.

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<sup>1</sup> With grant from Kong Christian X's Fond.



In order to eliminate these difficulties in preparing the fibrinogen, the authors on the basis of the knowledge that prothrombin is adsorbed to aluminiumhydroxyde, magnesiumhydroxyde, and tertiary calciumphosphat (1, 6), have prepared a fibrinogen containing solution from plasma by removing the prothrombin through adsorption with aluminiumhydroxyde. In the following a description is given of the technique used for the preparation of the fibrinogen solutions, both from ox plasma and from human plasma, and further the results obtained by using such plasmas, which contain fibrinogen, but are free from prothrombin, in Thordarson's coagulation system. As a standard was used a fibrinogen solution prepared from ox plasma by salting out with saturated ammoniumsulphate.

*Preparation of a fibrinogen containing solution from plasma by adsorption of prothrombin with aluminiumhydroxyde.*

1. *Human plasma.* Venous blood is drawn into a centrifuge tube containing powdered potassium oxalate (1 mg per ml blood). The sample is centrifuged for 10 minutes at 3500 revolutions per minute and the plasma is drawn off.

2. *Ox plasma.* 800 ml of blood is collected into 200 ml 1.85 per cent solution of potassium oxalate and centrifuged for 10 minutes at 3500 rev. per min. The plasma is drawn off.

3. *The suspension of aluminiumhydroxyde.* 5 grammes aluminiumhydroxide (Merck, pure, free of alkali) are suspended in 20 ml sodiumdiethylbarbiturate buffer (Michaelis' buffer as modified by Thordarson). The suspension is shaken well. By adding  $n/2$  HCl pH is made to 7.3—7.4 (determined with glass electrode, electrometer, »Radiometer», type PHM3).

4. *Adsorption.* 1 part aluminiumhydroxyde suspension is added to 2 parts plasma. The mixture is left for ten minutes during which it is frequently shaken with care; it is then centrifuged for five min. at 3500 rev. pr. min. The plasma is drawn off from the deposit. Ox plasma is adsorbed twice, the whole procedure taking place at room temperature. Plasma that has been adsorbed in this manner will — if frozen hard in closed phials — keep for a month.

In a coagulation system containing 0.3 ml thrombokinas solution, 0.3 ml calcium solution, 0.6 ml buffer, and 0.3 ml adsorbed

*A modification of the method for determining prothrombin described by Thordarson.*

A modification of Thordarson's method for determining prothrombin is described. Human plasma or ox plasma is depleted of prothrombin by adsorption with a suspension of aluminiumhydroxyde. By centrifuging the aluminiumhydroxyde settles, and the supernatant fluid is used as fibrinogen solution. When frozen had this solution keeps for a month. The same prothrombin values were obtained with adsorbed human plasma and with adsorbed ox plasma as with a fibrinogen solution prepared by precipitating the fibrinogen from ox plasma with a saturated solution of ammonium-sulphate.

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(From the Children's Ward of Aarhus Kommunehospital, Denmark. Chief:  
Professor Bent Andersen, M. D.)

## Heparin Blood and Landau's Micro Sedimentation Method.

By

GUNNAR NIELSEN and INGE RODE-MØLLER.

(Submitted for publication December 14, 1942).

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For determining the sedimentation rate in children and on the whole in cases where it is difficult to puncture a vein, and Westergren's method therefore cannot be employed, Landau's (1) modification of Linzenmeiers method has of late years been the one most in use here in Scandinavia. Landau's apparatus consists of a metal stand with 6 or 12 capillary tubes that may be supplemented with an exact syringe. The capillary tube has a length of 12 cm; its inside diameter is 1 mm. In the upper part of the tube there is a little ampoule; its lower part is provided with 2 marks, 12.5 and 62.5 mm, respectively, from the tip. The test is carried out in the following way: the capillary tube is fitted into the syringe, after which a 5 per cent sodium citrate solution is drawn up to the lower mark. Then blood taken from an incision in the finger-tip, the ear-lap or the heel is drawn up, until the mixture reaches the upper mark of the capillary tube. When the mouth of the capillary tube has been wiped off, the citrate blood is drawn up into the ampoule some times in order to be mixed, after which it is slowly «screwed» down into the capillary tube which is then placed in the stand. Reading off after 1 hour.

In recent years it has become common practice to use heparin blood for most routine blood tests with a single exception: it has

thus not previously been possible to use heparin blood for Westergren's sedimentation reaction, heparin blood partly giving a greater sedimentation rate, partly encumbering the method with greater defects (2). In an earlier work one of us has demonstrated (3) that it is possible to carry out the sedimentation reaction with heparin as anticoagulant and still obtain the same results as when Westergren's citrate method is used: A heparin concentration of 1 per thousand is necessary, and the blood must be diluted in the same proportion as by Westergren's method with a 0.5—0.7 per cent sodium chloride solution.

We have considered it desirable to carry out Landau's micro sedimentation reaction with heparin blood, and in a series of experiments with this we have replaced the 5 per cent citrate solution in its capacity of dilution fluid with a 0.6 per cent sodium chloride solution.

The procedure has been as follows: blood is taken from an incision in the ear-lap, the finger-tip or heel in a micro test tube ( $9 \times 40$  mm) prepared with  $0.2 \text{ cm}^3$  of a 0.05 per cent heparin solution in distilled water.<sup>1</sup> (Exsiccation in a hot-air stove at about  $100^\circ \text{C}$ .) In a Landau capillary tube a 0.6 per cent sodium chloride solution is drawn up to the lower mark. Then heparin blood is taken, until the mixture reaches the upper mark. Hereafter careful mixing in the ampoule and screwing down in the capillary tube in the usual way. Reading off after 1 hour.

We have carried out 65 experiments, where in each experiment from the same patient 1 Westergren macro sedimentation, 2 Landau citrate sedimentations and 2 Landau heparin sedimentations have been set up.

The results have been shown graphically in figure 1, where the abscissa states the sedimentation rate in mm after 60 minutes according to Westergren's method, whereas the ordinate shows the average value of the 2 Landau citrate sedimentations marked with a circle and the average value of the 2 Landau heparin sedimentations marked with a triangle, likewise in mm after 60 minutes.

As seen from figure 1, Landau's micro sedimentation method shows the same proportion to Westergren's macro method, whether it is carried out with citrate blood or with heparin blood. The

<sup>1</sup> In spite of the high price still ruling for heparin, such tubes with heparin dry substance can be produced in large quantities for less than 1 Öre per piece.

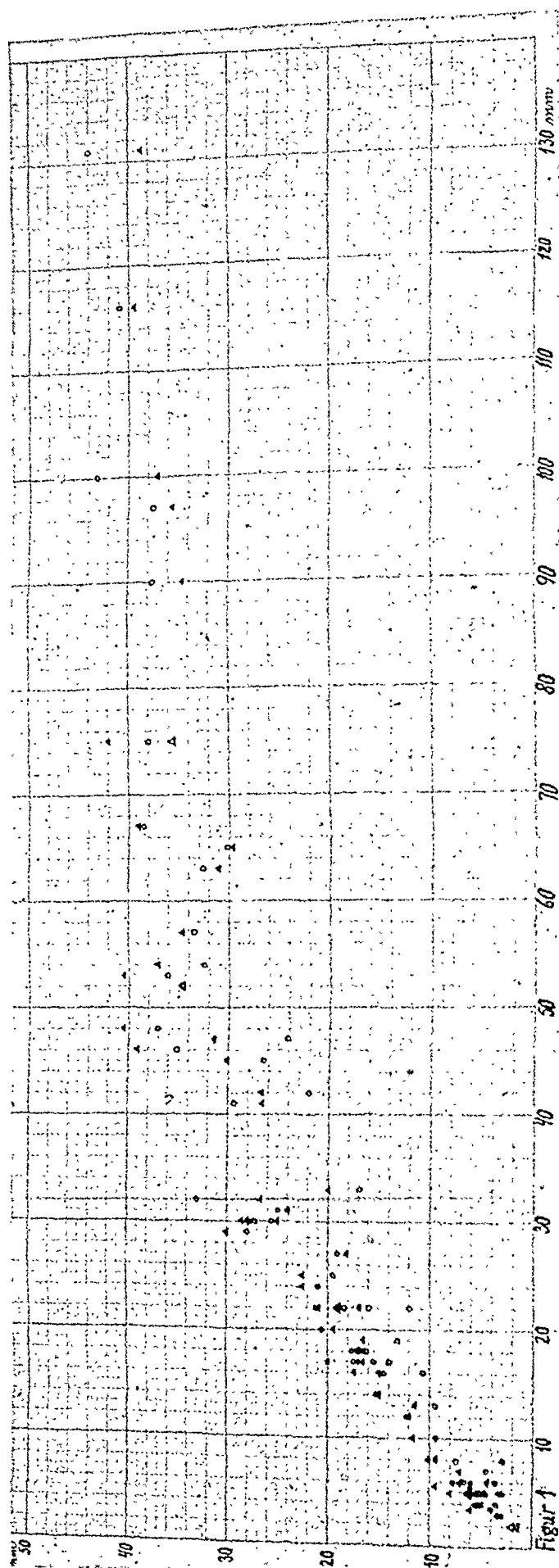


Fig. 1.

graduation of the sedimentation values stated by Landau for his citrate method: 1—8 mm for normal sedimentation reactions, 9—14 for slightly increased, 15—25 mm for increased, and over 25 mm for high sedimentation reactions, may be employed unreservedly, when the method is used with heparin blood diluted with a 0.6 per cent sodium chloride solution.

In order to elucidate the reliability of the two methods the difference between the double tests in the 65 experiments has been stated in table 1. It proves that about 93 per cent of the sedimentation reactions according to both methods give a difference of 2 mm and less.

Table 1.

| Difference between double tests | Number according to the citrate method | Number according to the heparin method |
|---------------------------------|--|--|
| 0 mm                            | 14                                     | 17                                     |
| 0.5—1                           | 29                                     | 28                                     |
| 1.5—2                           | 18                                     | 15                                     |
| 2.5—3                           | 2                                      | 3                                      |
| 3.5—4                           | 2                                      | 1                                      |
| 4.5—5                           | 0                                      | 1                                      |
| Total                           | 65                                     | 65                                     |

*Conclusion:* Experiments show that Landau's micro sedimentation reaction without losing in accuracy may be carried out with heparin as anticoagulant, when at the same time the blood is diluted with a 0.6 per cent sodium chloride solution. That is to say that it is now unnecessary on professional calls to convey the whole Landau apparatus to the patients or in the wards. The blood is only taken as for other routine blood tests in a tube prepared with heparin for later dilution and arrangement.

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based upon a larger series of observations. We are indebted to the clinical laboratory of the clinic for the technical performance of the tests, and to Dr. C. G. Holmberg and Dr. T. Stenstam for much good advice.

### Material.

The material comprised 86 cases. It does not include the 23 cases dealt with in the previous investigation. The 86 cases comprise the following:

Gastric ulcer, 24 cases

Duodenal ulcer, 44 cases

Gastritis etc., 18 cases.

The diagnosis was established along the usual lines, positive radiogram (including niche) being the condition for the diagnosis gastric or duodenal ulcer (except in one case, where the radiogram was fairly normal, but a typical ulcer was discovered in the minor curvature by gastroscopy). The diagnosis »gastritis etc.» refers to cases where no positive anatomical evidence of ulcer (such as radiography or gastroscopy) was to be observed, but where the history was more or less characteristic of ulcer: some of these cases applied for medical assistance because of melaena or haematemesis, and since, as a rule, these cases were not examined roentgenologically until the haemorrhage had ceased, they might or might not have represented ulcers; others might be termed »pre-ulcers» or »pseudo-ulcers», as in the previous study; as a rule they occurred in young individuals, mostly males, with a history of the characteristic ulcer type, with gastric hypersecretion and with negative radiograms as regards niche or deformations; the radiological evidence as to hypersecretion, on the other hand, seems extremely helpful and was frequently positive. Two cases of peptic ulcer had diabetes as well and were excluded, as were two others who had gone through a jaundice 10 years previously (in all these cases the galactose test was strongly positive).

The galactose tolerance test was performed according to the methods of Bauer (in 28 cases) or Malmros-Silver-Swaetichin<sup>1</sup> (in 58 cases). For details as to these methods, here termed B and M, respectively reference may be made to the previous study. The B-test is to be considered positive if the amount of sugar in the

<sup>1</sup> Swaetichin is identical with *Dr. Stenstam*.



urine exceeds 3 g, the M-test is positive if the blood sugar level rises above 0.18, but also if the amount in the urine exceeds 3 g. (Stenstam, unpublished observations). Owing to war conditions and the consequent difficulties of procuring galactose, we have not been able to perform the test during this last year, and for the same reason only one galactose test could be performed in most of the present cases. This is to be regretted, since it was demonstrated in the previous paper that, on the one hand, a positive M-test may be present in spite of a normal B-test, and on the other hand that a definitely pathological B-test was registered in 7 out of 8 cases where 3, or more than 3, determinations were made, whilst a similar response was to be elicited only in 1 out of 14 cases where less than 3 analyses were made. For this reason the number of positive observations in the present study represent a minimum, and the occurrence of a pathological galactose test in peptic ulcer is with certainty to be deemed more frequent than is indicated by the material here assembled.

Other tests applied during the present investigation were the citric acid test (cfr Sjöström and the paper by Ask-Upmark repeatedly quoted), the determination of bilirubin, the Takata test, the Rona test, the Quick test, and the pro-thrombin determination. The normal level of citric acid is indicated by Sjöström as ranging between 17 and 27; in the present investigation it is considered pathological if exceeding 30. The bilirubin test was not carried out as matter of a routine; it is here considered pathological if  $\geq 2$ . The Takata test was always negative, in almost all instances also the Rona test. With regard to the Quick test we have noted several pathological observations; they are not, however, included in the present investigation since we have induced a young Danish colleague, Knudsen, to cover this matter. The pro-thrombin tests will be presented in another publication by the present authors.

### Observations.

The material is briefly summarized in the following tables. The symbols are as follows.

Record: in the record series of the Medical Clinic.

Sex: M male, F female.

Age: when examined.

## I. Gastric ulcer.

## A. Positive B. Negative galactose test.

| Nr        | Sex | Age | His-<br>tory | Loca-<br>liza-<br>tion | Galactose tolerance |       |       | Ci/S | Bilirubin<br>n/200,000 |
|-----------|-----|-----|--------------|------------------------|---------------------|-------|-------|------|------------------------|
|           |     |     |              |                        | Test                | Urine | Blood |      |                        |
| A 2512/39 | M   | 37  | 1            | M                      | M 36.7              | 2.1   | 0.23  | 47.6 | 3                      |
| 2644/39   | M   | 52  | 1/12         | M                      | M 52.6              | 1.1   | 0.23  | 35.2 | —                      |
| 401/40    | M   | 65  | 0            | A                      | M 62.1              | 5.2   | 0.21  | —    | —                      |
| 1777/40   | F   | 65  | { Always     |                        | M 43.2              | 3.2   | 0.24  | 35   | —                      |
| 865/41    | M   | 46  | 3—4          | M                      | M 57.5              | 7.77  | 0.17  | —    | 3.05                   |
|           |     |     |              |                        | M 57.9              | 3.94  | 0.17  | —    | —                      |
| 938/41    | M   | 52  | 13           |                        | M 49                | 4.12  | 0.22  | —    | —                      |
| 2104/41   | M   | 49  | 30           | M                      | M 57                | 2.7   | 0.19  | —    | —                      |
| 2269/41   | F   | 64  | 1            | M                      | M 58                | 3.51  | 0.20  | —    | —                      |
| B 2395/39 | M   | 69  | 25           | M                      | B                   | 2.74  | —     | 34.4 | 0.6                    |
| 2396/39   | M   | 44  | 6            | M                      | B                   | 0.97  | —     | 36.0 | 0.6                    |
| 2417/39   | F   | 63  | 6            | M                      | M 36.5              | 1.43  | 0.17  | 33.6 | —                      |
| 2674/39   | F   | 68  | 20           | C                      | M 31.1              | 0.07  | 0.15  | 34   | —                      |
| 2730/39   | M   | 39  | 4            | M                      | B                   | 1.2   | —     | 32   | 1.1                    |
| 2876      | F   | 26  | 5            | M                      | M 48                | 0.24  | 0.14  | 36.3 | —                      |
| 3021/39   | F   | 41  | 24           | CM                     | M 43                | 1.22  | 0.17  | 38.8 | —                      |
| 182/40    | M   | 43  | 15           | P                      | M 49.3              | 0     | 0.13  | 35   | —                      |
| 519/40    | M   | 44  | 4            | M                      | B                   | 0.2   | —     | 42   | 0.5                    |
| 2063/40   | M   | 51  | 5            | C+B                    | B                   | 2.1   | —     | 26.2 | —                      |
| 3107/40   | F   | 41  | 15           | P                      | M 60                | 1.72  | 0.14  | —    | —                      |
| 883/41    | M   | 44  | 3—4          | P                      | M 48                | 1.41  | 0.16  | —    | 1.44                   |
| 1121/41   | M   | 41  | 11           | A                      | M 55                | 1.71  | 0.17  | —    | 0.8                    |
| 1092/41   | M   | 52  | 5            | M                      | M 42.2              | 1.93  | 0.18  | —    | 3.2                    |
| 2215/41   | F   | 51  | 2            | M                      | M 42                | 0.86  | 0.17  | —    | —                      |
| 2388/41   | F   | 46  | 20           | M                      | M 43.5              | 0.47  | 0.16  | —    | —                      |

History: first appearance of symptoms n years ago.

Localization: C cardia, M minor curvature (corpus), A angulus,

P pyloric region.

Galactose test: B = Bauer test, M = Malmros-Silver-Swaetichin test. (The figure appended = amount galactose administered).

Urine: amount of sugar in urine (Gm).

Blood: blood sugar level when maximal.

Ci/S: Citric acid test ad modum Thunberg-Sjöström.

For every case was also tabled the details of the history, the occurrence of complications (bleeding etc.), the gastric secretion (as judged from the fractional test meal, viz. by radiography),

## II. Duodenal ulcer.

## A. Galactose test positive.

| Record  | Sex | Age | History       | Galactose Tolerance |       |       | Ci/S | Bilirubin<br>n/200,000 | Remarks |
|---------|-----|-----|---------------|---------------------|-------|-------|------|------------------------|---------|
|         |     |     |               | Test                | Urine | Blood |      |                        |         |
| 2713/39 | M   | 43  | 2             | M                   | 3.35  | 0.20  | 25.2 | —                      |         |
| 2727/39 | M   | 33  | 8—10          | B                   | 3.5   | —     | —    | 2.8                    |         |
| 3207/39 | F   | 35  | {long<br>time | M                   | 45.7  | 1.67  | 0.21 | 34                     | 2.2     |
| 1169/40 | F   | 45  |               | M                   | 45.9  | 4.63  | 0.19 | —                      |         |
| 1412/40 | M   | 61  | 4             | M                   | 68.4  | 7.7   | 0.15 | 28.5                   |         |
| 2220/40 | M   | 27  | 1             | M                   | 52    | 9.1   | 0.21 | 26.9                   |         |
| 2429/40 | M   | 66  | 0             | B                   | 3.68  | —     | —    | —                      |         |
| 272/41  | M   | 61  | 5             | M                   | 68    | 5.81  | 0.16 | 23.7                   | 1.0     |
| 253/41  | F   | 34  | 2             | M                   | 45    | 3.37  | 0.18 | —                      | —       |
|         |     |     |               | M                   | 45.7  | 2.97  | 0.18 | —                      | —       |
| 330/41  | M   | 65  | 4             | M                   | 72    | 7.08  | 0.23 | —                      | —       |
| 512/41  | M   | 45  | 25            | M                   | 50.7  | 1.9   | 0.21 | —                      | —       |
| 575/41  | M   | 25  | 3             | M                   | 53.2  | 7.53  | 0.19 | —                      | —       |
| 596/41  | M   | 32  | 14            | M                   | 68.2  | 7.24  | 0.17 | —                      | 0.5     |
|         |     |     |               | B                   | 1.9   | —     | —    | —                      | —       |
| 2030/41 | M   | 40  | 10            | M                   | 40.8  | 3.73  | 0.21 | —                      | —       |
| 2246/41 | M   | 26  | 1             | M                   | 44.3  | 1.62  | 0.20 | —                      | —       |
| 2330/41 | M   | 44  | 21            | M                   | 47.7  | 1.73  | 0.19 | —                      | —       |
| 2370/41 | M   | 24  | 8             | M                   | 56.4  | 5.6   | 0.21 | —                      | —       |
|         |     |     |               | M                   | 56.4  | 5.75  | 0.21 | —                      | —       |
|         |     |     |               | M                   | 57    | 5.78  | 0.21 | —                      | —       |
| 2413/41 | M   | 33  | 10            | M                   | 54.3  | 3.82  | 0.18 | —                      | —       |
| 165/42  | M   | 44  | 15            | M                   | 48.9  | 4.59  | 0.19 | —                      | —       |
| 443/42  | M   | 53  | 22            | M                   | 41.7  | 0.8   | 0.19 | —                      | —       |

After treatment

After treatment

After treatment

" " +  
atropin 4 mg × 1

Achyilia resistant to histamine. Gastroscopy: normal conditions after treatment.

the gastric motility (occurrence of retention after 4 hours, etc.)  
the pulse rate (occurrence of bradycardia), and other items, but in  
order to save space these data are omitted.

A brief summarizing of the tables yields the following data:

*Methods.*

The galactose tolerance test was performed

ad modum B in 28 cases { 5 gastric ulcers; all negative  
17 duodenal ulcers; two positive  
6 gastritis etc; all negative

*B. Galactose test negative.*

| Record  | Sex | Age | History | Galactose Tolerance |       |       | Ci/S | Bilirubin<br>n/200,000 | Remarks   |
|---------|-----|-----|---------|---------------------|-------|-------|------|------------------------|---|
|         |     |     |         | Test                | Urine | Blood |      |                        |   |
| 2727/39 | F   | 22  | 0       | M 28.5              | 1.1   | 0.18  | 53   | 0.9                    | Previously operated upon<br>{ Achylia resistant to<br>histamine |
| 2773/39 | F   | 58  | 15      | M 50                | 0.69  | 0.15  | 41   | 1.1                    |   |
| 2792/39 | M   | 48  | 4       | B                   | 2.0   | —     | 50.5 | 1.6                    |   |
| 2854/39 | M   | 30  | 3       | B                   | 0.8   | —     | 29.7 | 4.4                    |   |
| 3041/39 | M   | 39  | 20      | B                   | 0.8   | —     | 40.6 | 0.5                    |   |
| 3074/39 | M   | 50  | 6       | B                   | 0.25  | —     | 66   | 1.4                    | 1936 ulcer perforans op.  |
| 3213/39 | M   | 24  | 0       | M 49.3              | 1.43  | 0.18  | 36.2 | 1.2                    |   |
| 301/40  | M   | 35  | 8       | B                   | 0.73  | —     | 40.0 | 0.8                    |   |
| 468/40  | M   | 53  | 4       | B                   | 0.1   | —     | 28.8 | 0.6                    |   |
| 481/40  | M   | 41  | 10      | B                   | 1.7   | —     | 35.7 | 0.45                   |   |
| 547/40  | M   | 62  | 0       | B                   | 0.3   | —     | 34.2 | —                      |   |
| 588/40  | M   | 64  | 4       | B                   | 0.84  | —     | 31.8 | 0.8                    |   |
| 771/40  | M   | 44  | 15      | B                   | 1.9   | —     | 50.5 | —                      |   |
| 848/40  | M   | 53  | 4       | B                   | 0.5   | —     | 16.2 | —                      |   |
| 884/40  | M   | 42  | 20      | B                   | 0.7   | —     | 26.4 | 0.3                    |   |
| 1033/40 | M   | 51  | 20      | B                   | 2.6   | —     | 34.3 | 0.4                    | Kissing ulcer   |
| 1119/40 | M   | 67  | 16      | B                   | 1.7   | —     | 27.9 | —                      |   |
| 1452/40 | M   | 22  | 2/12    | B                   | 1.6   | —     | —    | —                      |   |
| 1573/40 | M   | 38  | 10      | M 60                | 2.6   | 0.18  | —    | —                      |   |
| 2531/40 | M   | 30  | 6       | M 53.7              | 1.75  | 0.16  | —    | —                      |   |
| 2555/40 | F   | 44  | 2       | M 47.5              | 0.88  | 0.15  | —    | 0.7                    | ulcus perforans 1934  |
| 2763/40 | M   | 42  | 2       | M 46.4              | 2.48  | 0.18  | —    | 1.0                    |   |
| 1628/41 | M   | 59  | 6/12    | M 64.4              | 0.31  | 0.14  | 46   | 0.6                    |   |
| 2732/41 | M   | 31  | 7       | M 50.2              | 1.28  | 0.16  | —    | —                      |   |
|         |     |     |         | M 49                | 2.65  | 0.17  | —    | —                      |   |

ad modum M in 58 cases { 19 gastric ulcers; 8 positive, 11 negative  
 27 duodenal ulcers; 18 " 9 "  
 12 gastritis etc: 6 " 6 "

It will be seen that the test was positive in only 2 out of 28 B-tests, but in 32 out of 58 M tests. In all, a positive (i.e. pathological) galactose test resulted in 34 out of 86; for reasons already advanced, this figure represents a minimum, which probably might be considerably exceeded had the M-test been used in all cases, or at least the test repeated in the B-cases.

## III «Gastritis etc.»

(arranged according to age of patients)

| Record  | Sex | Age | History | Galactose Tolerance |       |       | Ci/S | Bilirubin<br>n/200,000 | Remarks |
|---------|-----|-----|---------|---------------------|-------|-------|------|------------------------|---------|
|         |     |     |         | Test                | Urine | Blood |      |                        |         |
| 1820/40 | M   | 20  | 3       | B                   | 1.4   | —     | 43.2 | 1.2                    | a       |
| 306/41  | M   | 20  | 1       | M 50.1              | 3.78  | 0.18  | —    | —                      | a       |
| 389/39  | M   | 21  | 1       | B                   | 2.62  | —     | 25.5 | 0.5                    | a       |
| 1539/40 | M   | 21  | 4       | M 48                | 3.6   | 0.19  | —    | —                      | a       |
| 1125/41 | M   | 23  | 1       | M 49                | 0.99  | 0.16  | —    | —                      | a       |
| 2462/41 | M   | 25  | 2       | M 57.6              | 3.25  | 0.15  | —    | —                      | a       |
| 2432/41 | F   | 28  | 15      | M 41.6              | 5.7   | 0.17  | —    | 0.6                    | a       |
| 2190/40 | M   | 39  | 0       | M 44                | 4.82  | 0.19  | —    | —                      | b       |
| 1818/41 | M   | 39  | 5       | M 92.8              | 0.19  | 0.14  | —    | —                      |         |
| 2382/40 | M   | 46  | 6/12    | M 74.6              | 1.38  | 0.16  | —    | —                      |         |
| 2460/39 | F   | 46  | 3       | M 43.6              | 1.95  | 0.19  | 40.8 | —                      | b       |
| 888/39  | M   | 48  | 8       | B                   | 1.79  | —     | 23.4 | —                      |         |
| 1688/41 | M   | 49  | 3       | B                   | 0.07  | —     | 24   | 0.65                   | c       |
| 583/41  | M   | 52  | —       | M 54.4              | 2.78  | 0.18  | —    | 0.4                    | d       |
| 1196/39 | M   | 53  | 6       | B                   | 2.3   | —     | 42   | —                      |         |
| 2126/40 | M   | 53  | 6       | B                   | 0.47  | —     | 32.5 | 0.2                    |         |
| 1419/41 | M   | 54  | 19      | M 75                | 1.21  | 0.18  | —    | —                      | b       |
| 221/40  | F   | 61  | 0       | M 41                | 0.48  | 0.15  | —    | —                      | b       |

a) Pre-ulcer or pre-ulcer-like condition

b) Gastric haemorrhage on admission, treatment, X-ray performed afterwards and negative

c) Achylia resistant to histamine. Gastroscopy: atrophied mucosa

d) Gastritis observed at gastroscopy

With regard to the M-test, it was positive in

|                      | Blood only | Urine only | Blood+Urine |
|----------------------|------------|------------|-------------|
| Gastric ulcer .....  | 3          | 1          | 4           |
| Duodenal ulcer ..... | 5          | 5          | 8           |
| Gastritis etc. ....  | 1          | 3          | 2           |
| In all. ....         | 9          | 9          | 14 cases    |

With regard to the amount met with in the urine, it was

|                      | < 1 gram | ≥ 1 < 2 gram | ≥ 2 < 3 gram | > 3 gram |
|----------------------|----------|--------------|--------------|----------|
| Gastric ulcer .....  | 7        | 8            | 4            | 5        |
| Duodenal ulcer ..... | 13       | 11           | 5            | 15       |
| Gastritis etc. ....  | 5        | 5            | 3            | 5        |
| In all .....         | 25       | 24           | 12           | 25       |

It should be observed that the M-test might be positive for the blood sugar also in cases where the amount excreted in the urine was  $< 1$  gram (one case),  $\geq 1 < 2$  gram (six cases),  $\geq 2 < 3$  gram (2 cases).

### *Sex and localization.*

#### *I. Gastric ulcers.*

|         |          | Galactose test | positive | negative        |
|---------|----------|----------------|----------|-----------------|
| Males   | 15 cases |                | 6        | 9               |
| Females | 9 "      |                | 2        | 7               |
| All     | 24 "     |                | 8        | 16 <sup>1</sup> |

#### *II. Duodenal ulcer.*

|         |      |    |                 |
|---------|------|----|-----------------|
| Males   | 38 " | 17 | 21              |
| Females | 6 "  | 3  | 3               |
| All     | 44 " | 20 | 24 <sup>2</sup> |

#### *III. Gastritis etc.*

|         |      |   |                 |
|---------|------|---|-----------------|
| Males   | 15 " | 4 | 11              |
| Females | 3 "  | 2 | 1               |
| All     | 18 " | 6 | 12 <sup>3</sup> |

An analysis of this table will show that 27 males out of 68, and 7 females out of 18, did present a positive galactose test, obviously no significant difference being present between the sexes. On the other hand, the duodenal ulcers presented a positive galactose test more often than the gastric ulcers (20 out of 44 as against 8 out of 24; if only the M tests are considered, we obtain 18 positive out of 27 duodenal ulcers, and 8 positive out of 19 gastric ulcers).

<sup>1</sup> The Ci/S test was positive in 5 of the galactose-negative males (6 cases thus tested) and in 3 of the galactosenegative females (3 cases tested). In one man 1092/41) the galactose test was negative, the Ci/S not carried out, but the bilirubin level markedly increased. In all, evidence of impaired liver function<sup>1</sup> was found in 12 males out of 15, and in 5 females out of 9, i.e. in 17 cases out of 24.

<sup>2</sup> The Ci/S test performed on 16 males and 2 females out of the 24 galactose-negative cases: in 11 males and 2 females it did exceed 30. In another male case, where the gal.test was negative and the Ci/S test only 29.7, the bilirubin was 4.4. Hence impaired liver function was registered in 34 out of 44 observations.

<sup>3</sup> In 6 males with negative galactose test, Ci/S was performed and was positive in 3, making a total of 9 out of 18 cases presenting either a positive galactose test or a pathological Ci/S test.

<sup>1</sup> Provided the galactose test depends upon this factor (cfr below).

*Age.*

With regard to the importance of age, the material is too limited to permit of any definite conclusions. It seems reasonable only to include the M tests, since the B tests, if negative and limited to one observation in every case, are open to criticism (*vide supra*). Hence the material will comprise 58 observations, in 46 of which positive evidence of a gastro-duodenal ulcer was obtained.

| Age          | Galactose test | Ulcers       |    |             |    |         |    |          |   |
|--------------|----------------|--------------|----|-------------|----|---------|----|----------|---|
|              |                | All 58 cases |    | Ulcers only |    | Gastric |    | Duodenal |   |
|              |                | +            | -  | +           | -  | +       | -  | +        | - |
| 20-29 .....  |                | 8            | 4  | 4           | 3  | 0       | 1  | 4        | 2 |
| 30-39 .....  |                | 6            | 4  | 5           | 3  | 1       | 0  | 4        | 3 |
| 40-49 .....  |                | 9            | 9  | 8           | 8  | 2       | 6  | 6        | 2 |
| 50-59 .....  |                | 3            | 6  | 3           | 4  | 2       | 2  | 1        | 2 |
| 60-69 .....  |                | 6            | 3  | 6           | 2  | 3       | 2  | 3        | 0 |
| In all ..... |                | 32           | 26 | 26          | 20 | 8       | 11 | 18       | 9 |

It is tempting to conclude that the occurrence of a positive galactose test is more frequent before 40 and after 60 than between 40 and 60 years of age, at least when gastric ulcers are concerned, but additional observations are needed to confirm this general impression.

*History.*

The duration of the history was found to be of no importance with regard to the occurrence of a positive galactose test. Positive as well as negative observations were registered in about the same proportion when the history was long and when it was brief. If only the M tests are considered, we obtain

| Duration of history (years) |                | $\leq 1$ | $> 1 \leq 5$ | $> 5 \leq 10$ | $> 10 \leq 15$ | $> 15$ |
|-----------------------------|----------------|----------|--------------|---------------|----------------|--------|
| Ulcer                       | Galactose test |          |              |               |                |        |
| Gastric .....               | +              | 4        | 1            | 0             | 1              | 2      |
|                             | -              | 0        | 4            | 1             | 3              | 3      |
| Duodenal .....              | +              | 2        | 6            | 4             | 3              | 3      |
|                             | -              | 3        | 2            | 3             | 1              | 0      |
| Gastritis etc. ..           | +              | 2        | 3            | 0             | 1              | 0      |
|                             | -              | 3        | 0            | 0             | 0              | 1      |
| In All .....                | +              | 8        | 10           | 1             | 5              | 5      |
|                             | -              | 6        | 6            | 4             | 1              | 4      |

As to the details of the history, particular attention was paid to the occurrence of night pains, hunger pains and seasonal periodicity. If only the M tests were employed, it was found that no conclusive difference in this regard was elicited for the gastric ulcers, possibly on account of the limited material available: a positive galactose test was about as common when night pains etc. were present in as when they were absent from the history. For the duodenal ulcers on the other hand the following observations were made:

|                      |         |                 |                                    |
|----------------------|---------|-----------------|------------------------------------|
| Night pains were     | present | in 10 cases, in | 8 of which the M test was positive |
|                      | absent  | 14              | 8                                  |
| Hunger pains were    | present | 14              | 8                                  |
|                      | absent  | 10              | 7                                  |
| Seasonal periodicity |         |                 |                                    |
| was                  | present | 13              | 11                                 |
|                      | absent  | 14              | 7                                  |

It will appear from these figures that the galactose test was to be expected to be positive particularly when seasonal periodicity or night pains were outstanding features of the history; if they were absent the M test might just as well be positive as negative, and the same thing holds for the hunger pains. It is obvious that these impressions must be substantiated by further research.

### *Bradycardia.*

The enigmatic occurrence of bradycardia with peptic ulcer was repeatedly noted also in this material. With regard to the behaviour of the galactose test in cases with bradycardia and without the following facts were ascertained. The analysis of the matter was confined to the gastric and duodenal ulcers. Cases with pronounced anemia in association with haemorrhage were excluded, since the pulse rate in such instances is obviously above the base line.

| Ulcer    | Bradycardia | Galactose test M |    | Gal. test B |   | In all |
|----------|-------------|------------------|----|-------------|---|--------|
|          |             | +                | —  | +           | — |        |
| Gastric  | Present     | 1                | 1  | 0           | 3 | 5      |
|          | Absent      | 7                | 8  | 0           | 2 | 17     |
| Duodenal | Present     | 7                | 1  | 1           | 6 | 15     |
|          | Absent      | 7                | 7  | 0           | 6 | 20     |
| Together | Present     | 8                | 2  | 1           | 9 | 20     |
|          | Absent      | 14               | 15 | 0           | 8 | 37     |



The following conclusions seem to be justified:

1. Bradycardia is more frequent with duodenal than with gastric ulcers. The same was the case with the positive galactose tests (cfr above).

2. Bradycardia is more frequent in cases with a positive galactose test ad modum M than in cases with a negative M test. If all positive galactose tests (thus also the positive B case) are considered, we have bradycardia in 9 cases out of 23, whereas the occurrence of bradycardia in the negative M test was restricted to 2 cases out of 17.

3. Bradycardia is quite frequently encountered also in cases with negative galactose test, provided that the method of Bauer is used (in 9 cases out of 17). For reasons already indicated above, it seems reasonable to assume that a great number of the galactose negative B tests might in reality represent positive galactose tests, had the test been repeated or replaced by a M test. The average amount of sugar excreted in the urine by the negative B cases with bradycardia exceeded the average amount excreted by the negative B cases without bradycardia.

Hence a certain congruity between the occurrence of bradycardia and the presence of a positive galactose test emerged.

#### *Gastric secretion and motility.*

The gastric secretion was, as a rule, examined by fractional test meal, which method, however, is inferior to the recently described method with continuous suction through a specially devised rubber tube (Lagerlöf-Ågren method; for references see Ihre). As a matter of fact, the occurrence of hypersecretion is hardly to be established with certainty except by the last-mentioned method, but certain evidence may nevertheless be afforded by the results of the fractional test meal, particularly if supplemented by the radiological observation of a hypersecretion (intermediary stratum); it cannot be too urgently emphasized that the clinician always should ask his roentgenological colleague about this matter in every individual case. An analysis of the material along these lines was carried out. As was to be expected, hypersecretion, high acidity and climbing curves were encountered more often with the duodenal than with the

gastric ulcers, quite frequently also in the cases designated gastritis. No conclusive difference could be established between the gastric secretion in the galactose-positive and the galactose-negative cases (in order to make the conditions as simple as possible, the material for this comparison was confined to the M tests in the gastric and duodenal ulcers, whereas the B tests and the gastritis case were excluded). Cases with pronounced hyper-secretion could be observed where the M test was positive, and others where it was negative; in (two M-tested) cases where achlorhydria refractory to histamine was present, the galactose test was positive once and negative once. The average acidity level (for free HCl) was higher for the gastric ulcers when the galactose test was positive, for the duodenal ulcers when the test was negative. Owing, however, to the objections to be raised against the method for the determination of gastric secretion, it was felt that this point must be taken up for further consideration in another study.

The data on the gastric motility were assembled mainly from the radiographic reports. The presence of a retention, even after 4 hours, did not seem to interfere with the result of the test. This is in agreement with our previous study on the subject, where it was demonstrated that the velocity with which the galactose was introduced into the duodenum was of no essential importance. In one case, however, the stomach was distended considerably, a large retention being present: in this case the amount of galactose in the urine was 0 g whereas the maximal blood sugar was only 0.13 g. In another case, not tabled here, a Billroth II had been performed 20 years before on a woman now aged 57; the emptying of the stomach was very rapid, and the galactose test was negative (amount in urine 1.3 g, maximal blood sugar 0.16).

#### *Autonomic pharmaea and galactose test.*

Care was taken in the great majority of the cases here observed to perform the galactose test before the commencement of any therapy. In some instances, however, the test was made during or after the treatment (bed, diet, remedies such as alkali, luminal, belladonna etc.). In a few instances, finally, (gastric ulcer 865/41, duodenal ulcer 253/41, 2370/41, 2732/41) the test was performed

repeatedly in the same case. In corroboration of our earlier experience in this matter, we found no significant difference between tests examined before and after the adoption of medication therapy. Since it was felt, nevertheless, that the effect of autonomic pharmacology ought to be studied in a more clear-cut way the following experiments were carried out.

1. In one selected case (2370/41, man, aged 24, duodenal ulcer) where the galactose test was markedly positive as well before as after the treatment, atropine was given during 4 successive days in a dose of  $0.5 \text{ mg} \times 8$ . The reaction with regard to heart-rate, salivation etc. was pronounced, but when the galactose test was again performed on the morning of the 4th day, the response was almost exactly the same as before. If it had changed, it would have been difficult to evaluate the effect, since according to our previous investigation the variability of the test is rather characteristic. Now it was in fact the same, which seems interesting enough.

2. To 3 healthy medical students (two men, one woman), aged 25—35, prostigmin was administered during 3 days in a dose of two tablets 3 times daily (in all 90 mg a day, per os). The galactose test *ad modum M* had previously been carried out and found normal. On the morning of the 4th day, 0.5 mg prostigmin was injected intravenously, whereupon the galactose test was repeated. Neither in the blood sugar curve, nor in the amount of sugar excreted in the urine was any significant change to be demonstrated: the response was as normal as before the prostigminisation.

It is perfectly obvious that experiments of this kind are open to criticism; the observations just described are only intended as a humble contribution to the subject.

### Comment and discussion.

In our earlier communication we maintained the view that the positive galactose test encountered with peptic ulcer should be ascribed to a functional disorder of the liver, reasonably closely connected with the nervous system. The present study seems to confirm this view, although it may be conceived that there are still matters which deserve further consideration. The analysis must take under consideration the following points.

1. The alimentary factor and the content of the gastro-intestinal canal.

2. The condition of the wall of the gastro-intestinal tract, i. e. the facilities for resorption.
3. The transport system of the galactose: the gastro-intestinal motility and the possibility of an Eck-mechanism.
4. The functional condition of the liver in peptic ulcer.
5. The behaviour of the tissues with regard to carbohydrates.
6. The excretion through the kidneys.

ad 1) Care was taken to avoid the source of error otherwise present in the Staub-Traugott phenomenon: on the one hand no carbohydrate starvation could reasonably be assumed to be present, on the other hand the administration of glucose, common in the therapy for peptic ulcer, was avoided prior to the performance of the test. The absorption of galactose from the alimentary canal is generally assumed to occur through the intestinal mucosa. The concentration of glucose in the bowels is believed to reach a relatively constant level, and the same may reasonably be the case with the galactose under ordinary conditions. If the distribution of water between the intestine and the blood is interfered with (as undoubtedly during the absorption of glucose) this shifting of water may be reflected in the blood sugar level. There is, to the best of our knowledge, no evidence available as to the behaviour of this factor in peptic ulcer and the matter no doubt deserves to be looked into. Another factor connected with the contents of the gastro-intestinal tract is the behaviour of the hydrogen ion concentration: if this is increased in the liver, glycogenolysis is apparently furthered and such an increase is believed to be brought about by the outflow of alkaline secretions into the intestinal canal (for references see Cantarow and Trumper). Since the gastric secretion with peptic ulcer is so frequently abnormal, it might not be unreasonable to pose the question whether the alkaline secretions into the intestine must not be accelerated in order to buffer the amount of acid available. This is a matter which merits further consideration. Since, however, a positive galactose test was found, even in the presence of achlorhydria resistant to histamine, it does not seem likely that this factor is of any but minor, if of any, importance.

ad 2) Whilst the ordinary absorption of galactose does occur through the intestinal mucosa, it might be possible that the common occurrence of hyperemia and oedema of the gastric mucosa in cases of peptic ulcer is liable to alter the permeability and facili-

tate the absorption. There are, however, three objections to be raised against this assumption. Firstly, the extreme variability in the amount of galactose eliminated in the individual case on different occasions strongly suggests a functional mechanism, not connected with any anatomical condition such as gastritis. Secondly, a markedly positive galactose test may be observed in instances devoid of any gastritis, as judged by gastroscopy. Thirdly, there is a rather characteristic inhibition of the response to galactose in several anemias (Stenstam, personal communications), and since these cases exhibit a pronounced gastritis, the contrary might have been expected, it being conceived that this gastritis ultimately assumes an atrophic character. It is an old observation that peptic ulcer may be observed in Addison's disease; the matter has been covered by one of us in a previous paper. Since according to Verzár, the phosphorylation of the hexoses in the intestinal mucosa, essential to the absorption, may be considered a function of the adrenal cortex, the possibility of adrenal insufficiency presents itself. It may, however, in at least most cases, be rejected: on the one hand, no other evidence along this line is to be elicited in peptic ulcer, on the other hand, it should, if present, have worked the other way, reducing the response to the ingested galactose.

ad 3) The increased irritability of the stomach with peptic ulcer (*Hyperergische Rezmagen*) might bring about a more rapid evacuation into the bowels, i. e. the absorption area, perhaps with resulting absorption of amounts of galactose liable to overcome the ordinary controlling capacity of the liver. On the one hand, however, it has been demonstrated in our previous paper that the abrupt introduction of galactose through a duodenal tube does not bring about any pathological response. On the other hand, the galactose test may be positive even in instances where a certain retention was present, and negative in cases where the stomach was rapidly emptied (e. g. in the Billroth II case mentioned above). With regard to the possibility of an Eck fistula mechanism, so commonly encountered in cirrhosis of the liver, no evidence is available in peptic ulcer as to the presence of such a mechanism, which seems entirely unlikely in cases devoid of any obstruction to the portal circulation.

ad 4) Abundant evidence is available of a disorder of the liver in connection with peptic ulcer. Experimentally, various types of

liver injury have been found to induce peptic ulcer in animals; a review of this matter will be found in our earlier communication. Clinically, the frequent involvement of the biliary system as described by Kalk, the elevation of the citric acid as investigated by Sjöström and ourselves, the occurrence of a positive Quick test not infrequently to be observed (unpublished observations, cfr above) afford convincing evidence. Since the galactose tolerance test, on the one hand, is one of our most reliable methods of detecting an impaired liver function, and on the other hand, is so often positive in peptic ulcer, it seems *a priori* reasonable enough to attribute the observations made in the present investigation to a functional involvement of the liver.

ad 5) The carbohydrate metabolism in peptic ulcer is liable to exhibit disturbances. Details in respect of this matter are to be found in our earlier paper. The salient point seems to be that the abnormal alimentary response to glucose which may be observed with peptic ulcer, has not been analysed with regard to its character, i. e. whether it is due to inadequate glycogen storage in the liver, to increased hepatic glycogenolysis, or to decreased tissue utilization. Investigations into this matter are scheduled; the general appearance of the blood sugar curve seems hardly to be compatible with the last-mentioned possibility, but rather to point towards the liver, but the serum phosphate concentration and the respiratory quotient are apparently matters calling for research in this connection. It is obvious, however, that if the carbohydrate metabolism in peptic ulcer is impaired, the galactose test may be liable to exhibit disturbances. Although, under normal conditions galactose is removed from the blood mainly by the liver, there seems to be some withdrawal of galactose by the tissues as well (vide Cantarow and Trumper). Even if it is decidedly more likely that a raised blood sugar level or melituria respectively after the administration of galactose is due to impaired liver function than to impaired tissue utilization the matter must be looked into.<sup>1</sup>

It is possible, although remaining to be decided, that the metabolic disturbances thus present in peptic ulcer may in some way be connected with the local reflex activities of the duodenopancreatic system. This possibility has been mentioned in our earlier paper

<sup>1</sup> The same is true for the question: how much of the raised blood sugar level depends on galactose, how much on glucose?

and has been considered also by Schnetz in his chapter on spontaneous hypoglycemia in the 7th vol. of *«Klinische Fortbildung»*. Schnetz calls attention to the occurrence of hypoglycemia in connection with duodenal ulcer, duodenitis and certain post-operative conditions (after resections of the stomach) and advances the opinion that the mechanism involved should be looked upon as some kind of *»dyskorrelatorische funktionelle Pancreopathien»*. It is perfectly obvious that an analysis of the pathological galactose tolerance test must pay all due regard to this matter; as emphasized above, however, further research along the metabolic line is needed.

ad 6) There seems to be no reason to assume any affection of the kidneys as being responsible for the positive galactose response encountered in peptic ulcer, since the elimination of galactose in the urine is apparently independent of its concentration in the blood, let alone other objections.

Briefly summarizing the analysis hence made, it may be said that the positive galactose test met with in peptic ulcer seems likely to be connected, on the one hand, with the functional impairment of the liver, on the other hand, with the disturbances of the carbohydrate metabolism. It is probable, although remaining to be established, that the last-mentioned factor is closely connected with the liver involvement (*vide supra*).

With regard to the interpretation of the liver involvement in peptic ulcer, this matter has been covered in our earlier paper on the subject, the conception being set forth that the liver disturbances are apparently parallel to, or under conditions prior to the ulcer in the sequence of events. The following salient features with regard to ulcer pathogenesis may be recalled.

1. The outstanding importance of the peptic factor is substantiated by numerous observations. Any factor, liable to reduce the resistance of the gastro-duodenal mucosa, such as starvation, malnutrition, deficiency syndroms caused by liver cirrhosis or by Addison's disease, infections, exposure to cold (not least of the feet!) invites the peptic activity of the gastric juice to carry out its destructive work, particularly of course if hypersecretion is present or induced, for example by nervous tension or mental worry in individuals constitutionally prone to react in that way.

2. The gastric secretion may be stimulated in various ways, but a most important factor seems to be the response to insulin. Con-

vincing evidence has been furnished indicating that insulin will stimulate the motor and secretory activities of the stomach, that this result will be obtained only if a certain hypoglycemia is obtained, that this hypoglycemia will exert its action on the stomach by means of the vagus centre, the impulses using the vagi to reach the gastro-intestinal tract, and that the gastric juice thus obtained by vagal stimulation includes an acceleration of the pepsin production, which has also been considered (by Ihre) to indicate the degree of vagal tonus. This series of observations will obviously facilitate the understanding, on the one hand, of the importance of the central nervous system in the ulcer pathogenesis (Ask-Upmark 1939), on the other hand, of the close functional relationships between the gastric secretion and the liver, since it has been demonstrated (by Kalk and Meyer and by Brühl) that the adequate response of the gastric secretion on insulin depends upon the functional condition of the liver. It may be added that, in as much as an increased vagal tonus may be assumed with peptic ulcer, the occurrence of bradycardia seems to be perfectly feasible.

3. The connections thus established between the peptic activities of the gastric juice and the effect of insulin is in itself suggestive of a disturbed carbohydrate metabolism in peptic ulcer. That such a disturbance really does exist has been demonstrated (Christlieb and others; cfr also the enigmatic hypoglycemias sometimes to be observed after surgical measures for gastro-duodenal ulcer). On the other hand, it may be maintained that the liver has a central position in the carbohydrate metabolism, and that liver disturbances of various kinds are also frequently to be encountered in peptic ulcer (*vide supra*). Considering this evidence and remembering also the correlations present between the liver and the central nervous system (*piqûre* etc.), it will appear that the peptic ulcer, viz. the gastric hyper-secretion was only one part of a functional disorder, ultimately no doubt of constitutional character, which manifests itself also by symptoms such as liver disturbances and bradycardia, and which reasonably has its primary instrument in the brain, probably in the hypothalamic region.

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Relationships have long ago been established in the evolution between the nervous system and the digestive tract. The stoma of the gastrula (in man: *canalis neurentericus*), the original de-



velopment of the nervous system as a network around the alimentary canal (as in several invertebrates), and the evolution of the pituitary system from the nervous system as well as from the Rathke pouch, are some of several evolutionary evidences available. It is only natural to find that region of the digestive tract which is of such paramount importance for the intake and preparation of food (gastro-duodenal segment, matrix of liver and pancreas) is functionally closely connected with that region of the brain which is so important for the preservation of life, the pituitary and hypothalamic region. As emphasized in our earlier paper, it seems reasonable ultimately to consider the peptic ulcer as an impairment of this system of correlations.

### Summary and Conclusions.

1. The galactose tolerance test was examined in cases of peptic ulcer. The material comprised 86 cases: 24 gastric ulcers, 44 duodenal ulcers, 18 cases designated gastritis («pre-ulcer» etc.). The method of Bauer was used in 28 cases («B-tests»), the method of Malmros-Silver-Swaetichin in 58 cases («M-test»). Other tests employed in the study were the citric acid test, the bilirubin determination, the Takata-test, the Rona test and the Quick test.

2. A positive galactose test resulted in 34 out of 86 cases. This figure represents a minimum, which probably might be considerably exceeded had the M test been used in all cases, or at least had the B test been repeated, which was not permissible under our working conditions (lack of galactose). The Malmros-Silver-Swaetichin test is far superior to the Bauer test, judging from the present investigation.

3. The galactose test was positive for 27 males out of 68 and for 7 females out of 18. The duodenal ulcers gave a positive test more often than the gastric ulcers (20 out of 44, as against 8 out of 24; if only the M tests are considered, we obtain 18 positive out of 27 duodenal ulcers and 8 positive out of 19 gastric ulcers).

4. Whether age has any influence on the positiveness of the galactose test in peptic ulcer seems uncertain. With regard to the history, its duration was found to be of no importance in this respect. The galactose test is to be expected to be positive particularly when seasonal periodicity or night pains were outstanding features

of the history, but it may be positive also in the absence of these symptoms.

5. Bradycardia is more frequent in duodenal than in gastric ulcers and more frequent in cases with a positive galactose test than in cases with a negative galactose test (ad modum M).

6. No conclusive evidence was adduced in this investigation as to any influence of the gastric secretion or the gastric motility on the galactose test. The test may be positive in cases with hypersecretion, but also when achlorhydria is present, it may be positive when the evacuation of the stomach is retarded and when it is accelerated.

7. The administration of atropin to a patient with positive galactose test did not affect the result, neither did the administration of prostigmin to 3 healthy individuals with negative galactose test.

8. These observations are discussed. The authors arrive at the conclusion that the positive galactose test in peptic ulcer is due to a functional involvement of the liver, although the test is hampered to some extent by certain disturbances in the carbohydrate metabolism occurring in peptic ulcer. These disturbances are probably to be ascribed to a liver involvement as well, but more research is needed into this problem. Abundant evidence is available, however, as to the functional impairment of the liver in peptic ulcer, as well experimentally as clinically. With regard to the present study, evidence of impaired liver function was afforded in 17 gastric ulcers out of 24, in 34 duodenal ulcers out of 44, and in 9 out of 18 cases designated gastritis (galactose test, citric acid test, bilirubin level). The bearing of these observations on the pathogenesis of peptic ulcer is briefly outlined, the importance of the nervous correlations being stressed.

### Bibliography.

Detailed references are to be had in the following papers: Ask-Upmark, E.: 1940, *Acta Med. Scand.* 103: 280—320. — Cantarow, A. and M. Trumper: 1939, *Clinical Biochemistry*, Saunder Co.

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From the Blegdamshospital (The University Clinic of Epidemic Diseases),  
Copenhagen. Physician-in-chief: Professor, Dr. H. C. A. Lassen.

## Involvement of the Central Nervous System in Mumps.

By

H. O. BANG and JENS BANG.

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### Chapter I.

Among the infectious diseases which occasionally are complicated by symptoms from the central nervous system, epidemic parotitis apparently occupies a special position, partly because of the frequency with which it is accompanied by complications of this kind, and partly because of the absolute predominance among these complications of benign lymphocytic meningitis.

In recent years much attention has been given to the post-infectious diseases of the central nervous system, which especially complicate a number of virus diseases. In case of epidemic parotitis in particular, this growing interest has led to a very copious literature. In Denmark, cases of meningitis parotidea have been recorded by Krabbe, Koefoed, Fuhrmann, Schiodt, Johansen and Nissen<sup>1</sup> — in Sweden by Wallgren, Bergmark, Ask-Upmark, Gedda, Nordwall, Linde, Silwer and Ahlberg. Silwer's investigation from 1936 deserves special mention, giving a comprehensive review of the subject, illustrated by his own material of 33 cases of meningitis

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<sup>1</sup> Since the present article was completed, Jersild has published a paper dealing with 16 cases of meningitis parotidea, 11 of them with meningitis as sole manifestation of parotitis infection. 10 cases of meningitis parotidea have been reported by Koch. Further, since the present article was set up, 111 cases have been described in this publication (1942, 112, 314) by Levison and Thordarson.

parotidea. More recently we find the work of Ahlberg, comprising 70 cases. In Norway, Ustved has recorded 7 cases.

In England and United States, Birnberg has collected 38 cases, Tabor and Newman 29, and Finkelstein 16; of minor scope is the work by Green and Heeren, Harris and Bethel, Bridgeman and Schwab. A comprehensive review and bibliography have been prepared by McKaig and Woltman. In France, papers on the subject have been published by Andrieu et al., v. Bogaert et al., Cathala et al., Dénéchau, Lemierre et al., Tokhadzé et al., and Urechia et al. An excellent review has moreover been published by Glanzmann, Switzerland. In Germany, investigations on the subject have been made by Jasinski and Schönfeld.

### *The etiology of mumps.*

It has been satisfactorily established that mumps is caused by a filterable virus which is pathogenic to various experimental animals. Thus the disease may be transferred to monkeys by inoculation into Steno's duct of filtered saliva from patients in the early stage of mumps. This saliva contains a filterable virus which produces an acute, non-suppurative parotitis in the monkey, analogous to the epidemic parotitis in man. The disease may be transferred from monkey to monkey, and the specificity of the virus is shown by transmitting the disease from the infected monkeys to human beings. Recovery from the infection leaves the monkeys immune (Johnson and Goodpasture, Findlay et al., Block, Levaditi et al.).

### *The etiology of meningo-encephalitis.*

There has been some disagreement regarding the etiology and pathogenesis of the post-infectious diseases of the central nervous system in virus diseases and post-vaccinal encephalitis. We shall not go into details about the theories proposed, but only mention the two most important of them: (1) That the involvement of the central nervous system is due to the virus of the primary disease itself (*in casu* the virus of mumps) — (2) That it is due to an unknown, latent, neurotropic virus, activated by the primary disease (mumps).

In case of mumps, the latter theory, which is purely speculative, is contradicted, for example, by the occurrence of the prodromal forms of meningitis, *i. e.*, cases where the meningitis precedes the parotitis, and by the so-called autonomic forms, *i. e.*, meningitis of parotitis virus etiology, but with no swelling of the parotid glands.

The first mentioned theory — that *the virus of the mumps itself* is the causative agent — seems reasonable a priori. It is supported by the frequent occurrence of meningitis in mumps, with only slightly varying symptoms, and also by the fact that the virus of mumps shows a strong tendency to invade other tissues besides the parotid glands. Thus the virus seems to possess a fairly pronounced neurotropy (a term which, however, should not be used without reservation, the term «mesodermotropy» being more correct when speaking of the pure forms of meningitis which in this case predominate).

Moreover, the theory has found *experimental support*:

Lavergne and co-workers claim to have produced meningo-encephalitis in rabbits by injection of spinal fluid from patients suffering from meningitis parotidea. The results should be accepted with some caution, however, since it is well known that rabbits are disposed to meningo-encephalitis, both spontaneously as well as after various intracranial operations. Other investigators have not succeeded in demonstrating virus in the spinal fluid from patients — a circumstance, though, which does not necessarily contradict the idea that the meningitis is caused by the virus of mumps; thus for example, it is impossible to demonstrate poliomyelitis virus in the spinal fluid, although it is present in the substance of the spinal cord.

Wollstein was able to produce a mild meningitis with filtered saliva from parotitis patients, by sub-occipital injection into cats; employing spinal fluid from these animals he could produce the disease in other cats by sub-occipital injection. Gordon injected filtered saliva from parotitis patients intracerebrally into monkeys, the reaction being a severe, and in a few cases fatal, lymphocytic meningitis.

By intracerebral inoculation of monkeys with filtered saliva from parotitis patients, Johnson and Goodpasture found no clinical symptoms of involvement of the central nervous system, but his-

topathological examination of the killed monkeys revealed inflammatory changes in the central nervous system, together with focal lesions in the parotid glands, and the monkeys inoculated in the cerebrum showed immunity when inoculated in the parotid glands. Even if these authors did not succeed in transferring the disease, it must nevertheless be considered very likely that the signs of the affection of the nervous system disclosed in the monkeys were due to the virus of the mumps.

### *Clinical types.*

The neurotropy of the parotitis virus is shown by its ability to affect practically all parts of the central nervous system, though with varying frequency.

1. *Meningitis* (benign lymphocytic) is the most common complication. The terms »para-» and »post-infectious» are used, according to whether the meningitis coincides with or occurs after the onset of the swelling of the parotid glands. The »prodromal» form is rarer — it applies to meningitis which precedes the swelling of the glands. Meningitis may also occur latently, *i. e.*, without any clinical symptoms and signs, only diagnosed by means of lumbar puncture (Finkelstein). Of special interest is the so-called »autonomic meningitis», *i. e.*, meningitis of the mumps virus etiology, but with no swelling of the parotid glands.

2. *Meningo-encephalitis and encephalitis* are rare and dangerous complications. Like meningitis they may occur before, during or after the parotid swelling (Andrieu et al.), most frequently, however, on the 8th to 10th day after the swelling (Glanzmann). The symptomatic picture is varied, including all types of paresis (paresis of the ocular muscles, facial paresis, hemiplegia, monoplegia) as well as acute ataxia, convulsions, coma and mental disturbances. Sequels may occur. Encephalitis has been observed by Schiodt, Johansen, Glanzmann, as well as by v. Bogaert et al. and by Urechia — in the latter cases accompanied by psychosis. Optic neuritis and atrophy of the optic nerve have been observed by Schwab.

3. *Myelitis* is a very rare complication. Cases with paraplegia, sensorial and sphinctorial disturbances have been described by McKaig and Woltman. Other data are given by Dénéchau and by Lemierre et al.

4. *Neuritis* (polyneuritis) is described as another very rare complication; perhaps it is here rather a question of polyradiculitis or meningo-radiculitis (McKaig and Woltman, Glanzmann, Cathala et al.).

*Complications from the internal ear* are well known. The pathology is unknown, but the question will be discussed in connection with one of our cases.

*The frequency of involvement of the central nervous system in mumps.*

Different views have been advanced regarding this question. The extremely wide divergencies in the statistics may be attributable to actual variations in the incidence of the complications of the central nervous system within different epidemics of mumps, but may also be attributable to the varying zeal with which these complications are traced. In this connection it should be borne in mind that the not infrequent cases of latent meningitis will escape recognition unless one resorts to routine lumbar puncture. According to Silwer, Radin and Sailer did not find a single case of clinical meningitis among 5,756 American soldiers suffering from mumps during the last world war. Nor was clinical meningitis observed among Iversen's 203 cases of mumps in soldiers. The frequency of involvement of the central nervous system is usually estimated at 4 to 25 per cent (Andrieu et al., Silwer). In our material from the epidemic of mumps during the winter 1941/42 this kind of complication was observed in 65 % of the cases.

### *Pathology.*

Death resulting from parotitic meningitis is rare, so that only few descriptions of the pathological findings exist. Linde found serous or serofibrinous, non-bacterial leptomeningitis with hyperaemia and oedema, especially localized at the base of the brain. Microscopical examinations revealed infiltration, chiefly mononuclear, into the pia and the arachnoidea.

According to Urechia, the rarer, but more frequently fatal cases of encephalitis are pathologically characterized by slight lesions of nerve cells, perivascular, predominantly lymphocytic infiltrations, neuroglial reactions, foci with demyelination and possibly small

capillary hemorrhages. Similar changes are reported by Wegelin. The histo-pathological findings thus have a likeness to the findings in smallpox and measles (Bang) and in post-vaccinal encephalitis. The earlier literature (1880—1928) on the pathology is cited by McKaig and Woltman.

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### *The authors' investigation.*

During the epidemic in the winter 1941/42 458 patients with mumps were admitted to the *Blegdamshospital* in Copenhagen. It was soon noticed that meningitis occurred with a considerable frequency, and spinal puncture was therefore adopted as a routine examination in order to determine how frequent the changes in the spinal fluid occurred. Lumbar puncture was applied to a total of 371, *i. e.*, 81 % of the patients with mumps. Only these patients are included in the material, the balance presenting nothing of interest.

When judging the frequency of involvement of the central nervous system it should be understood that the present material is not entirely free from selection, some of the patients being admitted to the hospital for the very reason of meningeal symptoms; a few others were admitted because their parotitis had taken a more severe turn, *e. g.*, had been complicated by orchitis. The majority of the patients, however, were admitted for uncomplicated parotitis at an early stage of the disease. The material may therefore, with these reservations, be considered a fairly representative section of the epidemic of mumps in Copenhagen during the winter 1941/42.

Our criterion for the diagnosis *manifest meningitis* is the presence of indisputable meningeal signs (stiffness of neck or positive Kernig and Brudzinski signs). Cases with spinal pleocytosis as the sole indicator of affection of the central nervous system are here termed *latent meningitis*. Cases with clinical symptoms and signs of meningitis, but without spinal pleocytosis, are termed *meningism*. When finding 3 cells or more per mm<sup>3</sup> of spinal fluid, we apply the term *spinal pleocytosis* to the case.

The cases are then divided into the following groups:



Table 1.

*Classification of cases.*

No. of cases

|  |     |
|--|-----|
| 1. Parotitis without complications from the central nervous system ..... | 126 |
| 2. Parotitis with manifest meningitis .....                              | 106 |
| 3. Parotitis with latent meningitis .....                                | 129 |
| 4. Parotitis with meningism .....  | 10  |
| 5. Parotitis with meningitis and affection of the labyrinth .....        | 1   |

The case with affection of the labyrinth will later be considered separately. The numerically insignificant group of meningism will not be included in the evaluation of the material.

There remain the large groups 1, 2 and 3, with a total of 361 cases. Of these, 235 (65 %) were affected with meningitis, 106 (45 %) being manifest, 129 (55 %) latent. The manifest meningitis occurred in about 30 % of the total of 235 cases of mumps.

*Age and sex.*

Table 2.

Distribution according to age and sex. Frequency of pleocytosis within the different age-groups and within the total number of patients with mumps.

| Age years | Total number of cases | Cases without pleocytosis | Cases with pleocytosis | Pleocytosis in per cent of the total in each age-group |
|-----------|-----------------------|---------------------------|------------------------|--|
| 0—1       | ♂ 17<br>♀ 5           | ♂ 9<br>♀ 3                | ♂ 8<br>♀ 2             | ♂ 47<br>♀ 40   |
| 2—5       | ♂ 55<br>♀ 36          | ♂ 18<br>♀ 15              | ♂ 37<br>♀ 21           | ♂ 67<br>♀ 58   |
| 6—14      | ♂ 69<br>♀ 40          | ♂ 18<br>♀ 15              | ♂ 51<br>♀ 25           | ♂ 74<br>♀ 62   |
| 15—25     | ♂ 26<br>♀ 41          | ♂ 10<br>♀ 16              | ♂ 16<br>♀ 25           | ♂ 62<br>♀ 61   |
| above 25  | ♂ 39<br>♀ 33          | ♂ 11<br>♀ 11              | ♂ 28<br>♀ 22           | ♂ 72<br>♀ 67   |
| Total     | ♂ 206<br>♀ 155        | ♂ 66<br>♀ 60              | ♂ 140<br>♀ 95          | ♂ 68<br>♀ 61   |

Table 2 shows that there are more male than female patients and that there does not seem to be any conclusive difference between the frequencies of the involvement of the central nervous system in the two sexes when taking all age-groups into account. Within some of the age-groups the frequency of the complications seems higher in case of the male patients, but the difference is not sufficiently large to be of any significance.

### *The spinal fluid.*

The first lumbar puncture was performed as soon as possible after admission. The possible error arising from the circumstance that the patients were admitted at different stages of their disease was to some degree compensated for by performing the lumbar puncture, in the vast majority of cases, more than once during the disease. When pleocytosis was ascertained, the cell count in the spinal fluid was studied by means of repeated lumbar punctures during the whole stay in the hospital, frequently up to 6 to 7 times, in order to get an idea of the course of the changes. When there was an opportunity to watch the changes in the spinal fluid from their beginning, the typical course was found to be that the cell count rose rapidly from normal to maximal values, then fell rapidly again to slightly increased values (usually below 30 per  $\text{mm}^3$ ), whence the fall to normal values occurred slowly, in many cases so slowly that the patient had to be discharged before normal values were reached.

In all cases the *pleocytosis* was purely or predominantly lymphocytic.

In by far the most cases the *proteins* showed no increase, or only a small one. Even at high cell counts the proteins, in comparison with the magnitude of the pleocytosis, were upon the whole less changed than one would expect from a comparison with other forms of lymphocytic meningitis. In all cases the *sugar* was normal, the *Wassermann reaction* negative, and the *spinal fluid cultures* negative.

### *The degree of the pleocytosis.*

While all degrees of pleocytosis were found, there was nevertheless a striking frequency of the higher cell counts. Table 3

Table 3.

Distribution according to the degree of pleocytosis.

| Cells per 3 cu. <sup>1</sup><br>mm spinal fluid | Total number of<br>cases of<br>pleocytosis | Cases with manifest<br>meningitis |          | Cases with latent<br>meningitis |          |
|---|--|-----------------------------------|----------|---------------------------------|----------|
|   |  | Number                            | per cent | Number                          | per cent |
| 10—19   | 35   | 7                                 | 7        | 28                              | 22       |
| 20—49   | 25   | 5                                 | 5        | 20                              | 15       |
| 50—99   | 20   | 7                                 | 7        | 13                              | 10       |
| 100—200   | 18   | 7                                 | 7        | 11                              | 9        |
| 200—500   | 44   | 20                                | 18       | 24                              | 19       |
| 500—1 000                                       | 37   | 21                                | 19       | 16                              | 12       |
| 1,000—2,000                                     | 27   | 19                                | 18       | 8                               | 6        |
| 2,000—5,000                                     | 28   | 19                                | 18       | 9                               | 7        |
| 5,000—10,000                                    |  |                                   |          |                                 |          |
| 10,000—20,000                                   | 1  | 1                                 | 1        |                                 |          |
|   | 235  | 106                               | (106)    | 129                             | (100)    |

<sup>1</sup> In Denmark the spinal cell count is usually expressed in cells per 3 cu. mm.

shows that the cell count in the spinal fluid apparently was higher in manifest than in latent meningitis. Although this fact is really not surprising, it is mentioned here because other investigators have claimed that there is no relation between the degree of pleocytosis and the presence or absence of clinical meningitis symptoms. It should be emphasized, however, that high cell counts were also noticed among the cases of latent meningitis, 17 patients having from 300—1000 cells per mm<sup>3</sup>.

#### *The time of the onset of meningitis.*

As far as the cases of manifest meningitis are concerned, table 4 shows the relation between the onset of the parotid swelling and the first clinical symptoms of meningitis. The table contains 104 cases in which this relation was accurately established, the cases being classified according to the number of days between the onset of the swelling and the appearance of the meningitis.

The table shows that the meningitis may appear *before, simultaneously with, or after* the swelling of the parotid glands. In the majority of the cases the meningitis appeared within the first 10 days after the swelling began, the maximum falling on the 5th day.



rarer in latent meningitis. *Bradycardia*, which in the literature is mentioned as an important symptom, was observed in only 25 % of the cases of manifest, and in only 14 % of the cases of latent meningitis. *Lethargy* was observed in 12, and *convulsions* in 2 of the cases of manifest meningitis. *Fever* constantly accompanied the meningitis, the initial high temperature either remaining stationary or, when the meningitis developed later, showing a secondary rise.

*Relation between the severity of the parotitis and the occurrence of meningitis.*

The degree of the parotid swelling, the fact that it was unilateral or bilateral, and its duration proved to be of no significance as far as the appearance of the meningitis was concerned. It was not primarily cases of severe parotitis which were exposed to complications from the central nervous system. The presence of *other complications of parotitis* was likewise without any importance to the development of meningitis, as shown by table 5.

Table 5.

The relation between meningitis and other complications of parotitis.

|                              | Number of cases | Submaxillary swelling |          | Pancreatitis |          | Number of males $\geq 13$ yrs. | Orchitis |          |
|------------------------------|-----------------|-----------------------|----------|--------------|----------|--------------------------------|----------|----------|
|                              |                 | Number                | Per cent | Number       | Per cent |                                | Number   | per cent |
| Cases without meningitis.... | 126             | 11                    | 9        | 3            | 2        | 25                             | 17       | 68       |
| Cases with meningitis ....   | 235             | 16                    | 7        | 5            | 2        | 49                             | 32       | 65       |
| Total .....                  | 361             | 27                    | 7        | 8            | 2        | 74                             | 49       | 66       |

The table shows the frequency of *submaxillary swelling*, *pancreatitis* and *orchitis*, and it is seen that these complications occurred with about equal frequency in the groups with and without meningitis. Thus the occurrence of one or more of these complications of parotitis did not increase the risk of further complications by an involvement of the central nervous system. It is moreover seen from the table that while submaxillary swelling and pancreatitis were

rare, orchitis occurred with considerable frequency, viz., in 66 % of all males above 13 years; below this age orchitis was not observed.

*Diastasuria* occurred in 230 cases, or 63 % of all patients examined.

### *Parotitic meningitis with affection of the labyrinth.*

As mentioned in the review of the material, one case of mumps was complicated by meningitis and affection of the labyrinth. Since this case is of particular interest it will be cited here in brief:

It was the case of a 31 year old unmarried female physician. She was admitted on January 30th. and discharged on May 5th. 1942.

Her *past history* was mainly of good health.

*Present illness:* 6 days before admission to the hospital there was a slight rise in temperature, with bilateral swelling of the parotid glands, the swelling, however, disappearing within 4 days. The day before admission the temperature rose to 39.5° C, accompanied by chills, headache, vomiting and deafness of the left ear.

*Physical examination on admission:* Temperature normal, swelling of both submaxillary glands, hardly any swelling of the parotid glands. Stiffness of the neck.

*Otological examination:* Reduced hearing of the left ear. After a few days total deafness of this ear. No sign of otitis.

On the 5th. day in the hospital the patient complained of vertigo. There was nystagmus to the right. The neck rigidity had disappeared.

On the 13th. day the nystagmus had disappeared. Examination of the labyrinth showed totally obliterated leftsided function.

During the following period the patient had to remain in bed; little by little she practiced sitting, and in 2 months she was out of bed again. The gait was at first staggering, wide, with a tendency to fall towards the left (as also shown in Romberg's test).

At discharge the patient still suffered from dizziness and must walk with a cane.

*Other examinations:* The temperature was normal during the stay in hospital. Urine without pathological components. Haemoglobin percentage 93. Diastase count 1,200 at time of admission, 400 six days later. It is unfortunate that no lumbar puncture was done. X-ray examination of the paranasal air sinuses showed nothing abnormal.

*Comment:* The case is that of a 31 year old woman who suffered an attack of mumps, and on the 5th day of illness, before the swelling of the parotid glands had subsided, developed meningeal

symptoms. The acute symptoms disappeared within a week, leaving vertigo and deafness of the left ear. Otological examination showed obliterated leftsided function of the labyrinth. The deafness was unchanged at a later examination 6 month after the parotitis; the vertigo had almost disappeared except at sudden movements.

Deafness after mumps is a well known and feared complication, but fortunately rare. According to Hubbard, 3—5 % of all deaf-mutism in United States is due to parotitis. There are different opinions regarding the *pathogenesis*. Thus the complication is attributed to an encephalitic process, an internal otitis, a toxic neuritis of the auditive nerve (Urbantschitsch), an involvement of this nerve by the meningitic processes (Ask-Upmark, Fuhrmann, Voss), or a sudden exudate in the labyrinth (McKaig and Woltman). If the affection of the labyrinth is due to an involvement by meningeal processes, it seems peculiar that this complication has been observed but once among our 236 cases of parotitic meningitis.

The prognosis of the parotitic deafness is poor.

An earlier parotitis will always be a possible etiologic factor in case of deafness of unknown origin.

## Chapter II.

### *Meningitis parotidea without parotid swelling.*

Earlier epidemics of mumps have occasionally led to the idea that meningitis might occur as the sole symptom of a parotitic infection. Such cases of meningitis parotidea without swelling of the parotid glands have been described as *autonomic forms*, — «meningo-encephalite ourlienne autonome» (Weissenbach et al.) or «meningite ourlienne sans oreillons» (Wallgren). It seems obvious that a diagnosis like this one must be subject to certain stringent requirements; the criteria will be discussed later. A few cases of this type of meningitis have been reported in Sweden (Wallgren 2 cases, Ask-Upmark 1, Silver 1, Linde 2 and Ahlberg 2). Elsewhere 2 cases have been described by Birnberg, 1 by Urechia and Elekes. Ahlberg has cited a few cases from the literature. In Denmark, Johansen has reported 1.<sup>1</sup>

<sup>1</sup> In a paper by Jersild, published after this article had been written, we find 11 cases of parotitic meningitis without swelling of the parotid glands. See footnote p. 487.

During the epidemic of mumps in 1941/42 a number of patients were admitted to the Blegdamshospital for observation of meningitis or fever of unknown origin. In some of these patients there was demonstrated latent or manifest meningitis, benign lymphocytic, and of unknown etiology. Since these cases, both in development and with respect to the changes in the spinal fluid, had a striking resemblance to parotitic meningitis, and since the patients moreover had been exposed to parotitic infection before admission, it was suspected that this meningitis might be of parotitis virus etiology.

It was a question of 18 patients who showed no swelling of the parotid glands. Of 5 of them it was learned on careful questioning that there was a possibility of a very slight parotitic infection prior to admission. They reported, for example, slight soreness during mastication, soreness in front of the ear, or a dubious facial swelling for a single day. The information showed that parotitic infection during the anamnesis could not be excluded, and the patients were therefore not included in the material.

Of the remaining 13 cases which were of special interest, 6 were of latent and 7 of manifest meningitis where parotid swelling both before admission as well as during the stay in the hospital could be definitely excluded. When we nevertheless regard these cases as parotitic meningitis it is because of the following facts:

1. All the patients had been exposed to parotitic infection for a period corresponding to the period of incubation. In by far the most cases one of several members of the family suffered from mumps.

2. None of the patients had had mumps before.

3. The cases coincided in time and place with the epidemic of mumps.

4. The clinical picture and the changes in the spinal fluid showed a striking resemblance to parotitic meningitis.

5. There was no other etiology. The season, which in all cases was December-February, did not suggest that it was a question of meningitis of poliomyelitic nature. The negative results of the Wassermann's, Bunnell's, Weil's and Widal's tests made it impossible that the origin should be syphilis, infectious mononucleosis, Weil's disease, or undulant fever — diseases of which it is known that they may be accompanied by a lymphocytic meningitis.



**Table 6.**  
13 cases of meningitis of parotitis virus etiology without parotid swelling.

| 13 cases of meningitis of parotitis virus etiology without parotid swelling |      |                  |                      |          |           |              |            |       |                |                        |                                      |                          |   |                               |                    |                            |                              |                  |                    |     |     |     |
|---|------|------------------|----------------------|----------|-----------|--------------|------------|-------|----------------|------------------------|--------------------------------------|--------------------------|---|-------------------------------|--------------------|----------------------------|------------------------------|------------------|--------------------|-----|-----|-----|
| Duration of fever (days)  |      | Maximum of fever |                      | Orchitis | Diastasia | Spinal fluid |            |       |                |                        |                                      | Other symptoms and signs | Rigidity of neck and pos. Kernig's sign | Degree of manifest meningitis | Type of meningitis | Duration of disease (days) | Day of disease when admitted | Exposed to mumps | Month of admission | Age | Sex | No. |
|   |      | Degrees Celsius  | on -- day of disease |          |           | Cultivation  | Sugar mg % | Pandy | % mononuclears | Cell count per cu. mm. | Lumbar puncture on -- day of disease |                          |   |                               |                    |                            |                              |                  |                    |     |     |     |
| 19  | 40   | 14               | 40                   | —        | —         | —            | —          | 65    | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   | —   |
| 13  | 39.9 | 6                | 39.9                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 7   | 38.5 | 3                | 38.5                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 11  | 39.7 | 7                | 39.7                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 14  | 40.5 | 4                | 40.5                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 8   | 40.7 | 9                | 40.7                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 10  | 40.5 | 4                | 40.5                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 12  | 39.8 | 2                | 39.8                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 8   | 40.6 | 3                | 40.6                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 9   | 40.1 | 4                | 40.1                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 7   | 39.8 | 3                | 39.8                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |
| 11  | 39.8 | 3                | 39.8                 | —        | —         | —            | —          | —     | —              | —                      | —                                    | —                        | —                                       | —                             | —                  | —                          | —                            | —                | —                  | —   | —   |     |

6. Diastasuria was found in 7 of the 13 cases, a fact which strongly supports the idea of interdependence with epidemic parotitis, without the absence of diastasuria in the remaining 6 making it improbable. (As mentioned in the foregoing chapter, diastasuria occurred in 63 % of all parotitis patients examined). Orchitis was found in 2 of the patients.

The table reviews the 13 cases which fall into 2 groups: 6 with latent meningitis, *i. e.*, with spinal pleocytosis as the sole indication of the meningeal affection — 7 with manifest meningitis, *i. e.*, with clinical meningitis signs (stiffness of neck and positive Kernig's sign) in addition to spinal pleocytosis.

The material comprises 9 male and 4 female patients in the age from 1 to 32 years. The patients had been ill from 2 to 14 days prior to admission.

Of the 7 cases of manifest meningitis, 2 were severe and 5 mild. The duration of the clinical meningitis symptoms was from 1 to 17 days. Headache and vomiting was found in nearly all of the 13 cases, lethargy in one and convulsions in one (a 1 year old child). There were no focal symptoms. As mentioned, orchitis occurred in 2 cases.

The spinal fluid showed increases in cell count of varying degree, higher cell counts occurring especially among the cases of manifest meningitis, lower counts among the cases of latent meningitis. The highest cell count was more than 1000 per mm<sup>3</sup>. The pleocytosis was completely or quite predominantly mononuclear. Protein values were normal or moderately increased, spinal sugar was normal, and no bacteria were found, either on direct microscopy or on cultivation.

All cases were febrile from the first day of the disease; the table shows the duration and maximum of the fever.

The prognosis was good; all patients recovered without sequels.

## Summary of Chapter I.

The question of involvement of the central nervous system in mumps has been reviewed and consideration given to the problems of frequency, etiology, pathogenesis, clinical types and pathology.

The review includes an account of the patients with mumps who were admitted to the Blegdamshospital during the epidemic of

1941/42. Routine spinal punctures were performed on 372, or practically all of these patients.

Among the 372 patients, spinal pleocytosis (*i. e.*, 3 cells or more per mm<sup>3</sup>) was observed in 235, or 65 %.

Of these 235 cases of pleocytosis, 106 showed *manifest*, 129 *latent meningitis*, *i. e.*, with pleocytosis as the sole indication of affection of the central nervous system.

There was no age of predisposition to meningitis, and both sexes were equally susceptible. The severity of parotitis, and the presence of other complications were of no importance with respect to the development of meningitis.

The magnitude of the pleocytosis varied between 3 and 7000 cells per mm<sup>3</sup> of spinal fluid; rather high cell counts were frequent, also among the cases of latent meningitis. The pleocytosis was entirely or predominately mononuclear. The proteins were not increased, or only moderately so, the spinal sugar was normal, the spinal fluid sterile.

*Manifest meningitis* appeared most frequently *after* the onset of the swelling of the parotid glands (up to 38 days after, but mostly about the 5th day), occasionally *simultaneously with*, and in some cases (10 %) *before* the swelling (up to 7 days before).

As a rule, the clinical meningeal symptoms were mild and of short duration.

Encephalitis and myelitis were not observed.

One case showed affection of the labyrinth as a complication of parotitic meningitis. Unilateral deafness persisted.

All the remaining patients were discharged without sequels. Thus the immediate prognosis of parotitic meningitis was *quo ad vitam* always good, and *quo ad restitutionem completam* almost without exception good. The late prognosis may be elucidated by a future examination of these patients.

The extremely high frequency with which meningitis occurs in our material (in about two-thirds of the cases) naturally raises the question of whether meningitis should not be considered a manifestation rather than a complication of parotitis. This suggestion finds support in the occurrence of the so-called prodromal forms where the meningitis precedes the parotitis, and the autonomic forms, of meningitis of parotitis virus etiology, but without swelling of the parotid glands. The latter type is dealt with in chapter II.

Mumps should undoubtedly be considered a general infection whose essential clinical manifestation most frequently, but not necessarily always, is a swelling of the parotid glands.

### Summary of Chapter II.

During the epidemic of mumps in 1941/42 13 patients with benign lymphocytic meningitis were admitted to the Blegdamshospital. The disease was in all probability of parotitis virus etiology, but without parotid swelling. Thus parotitis virus seems capable of affecting the meninges as the sole organ. Epidemic parotitis must therefore be considered a possible etiologic factor in cases of lymphocytic benign meningitis of unknown origin.

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<sup>1</sup> The original article has not been available.

(From the Consulting Bureau on Rheumatic diseases, Amsterdam, medical-director J. van Breemen.)

## **Spondylarthritis ankylopoetica (Spondylosis rhizomelica) combined with periferal Arthritis.**

By

H. J. N. DEKKERS, M. D.

(Submitted for publication September 16, 1942).

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### **Introduction:**

Spondylosis rhizomelica is a relatively seldom occurring disease. During the clinical years of the medical education most of us probably have seen only a few cases. Likewise a great deal of the general practitioners will see during their whole medical life only a few patients suffering from this disease.

To the seldom occurrence, together with the difficulties of identification, especially in earlier centuries, the remarkable fact must be ascribed that, although the spondylosis rhizomelica exists already during many centuries, and in anatomical museum preparations of columnae vertebrales, can be seen dating from the 17th and 18th century showing the classical anatomic signs of the disease, only at the end of the 19th century the attention was drawn to the clinical picture by French (Pierre-Marie), Russian (Bechterew) and German (Strümpell) clinicians. After this the occurrence of the spondylosis appeared to be more frequent than was at first believed. Since then an excessive number of publications has been devoted to the diag-

nosis, treatment, prognosis, morbid anatomy, pathogenesis and roentgenological aspects.

The diagnosis of the classic forms which have come to full development, is in general very simple. At the beginning of the disease a greater diagnostic skill, a greater experience as well as a permanent awareness of the condition is required. Without these many cases in the first stadium are overlooked readily, the more because at the beginning of the disease the diagnosis cannot be made with certainty without further investigation (X-ray pictures, examination of the blood, exact examination of the functions of the spine etc.).

Hare (1) in a recent publication once again mentioned the difficulties of early diagnosis. He divides the clinical course into three stadia:

*firstly:* the early so called »praespondylitic» phase, during which the patients only complain of vague pains of the back, extremities, chest and periferal joints. Because during this phase no roentgenological anomalies are yet present, no exact diagnosis is possible at this moment.

*secondly:* the sacroiliitic phase, during which the patients complain of pains during the night and in rest. By means of roentgenological examination a diagnosis is possible. An exposure of the sacroiliac joints shows as the only objective sign of the disease osteoporosis and affection of the sacro-iliac joints. Other objective signs may be completely absent at this time and by clinical examinations it is impossible to make the diagnosis. Between the beginning of the 1st and 2nd phase a space of time of three years may elapse.

*thirdly:* the end phase of the »pokerback» with more or less total stiffening of the vertebral column with bamboo-formation. In this phase the evaluation of the diagnosis gives no difficulties anymore.

Seen in this light one cannot wonder at the fact that the disease is diagnosed most times only 3—6 years after the beginning of the anomaly, according to Lassen (2) and Eltze (3); a fact which corresponds also with our experience.

Although relatively seldom occurring, the disease is by no means a rarity. This may be clear from the fact that in our centrum where of course the cases accumulate, during the past decade, from 1931 till ultimo 1940, 120 cases of spondylosis rhizomelica have been obser-

ved amongst the 27031 patients who sought relief for rheumatic affections, i. e. grossly said 12 per annum (see table 1); 10 of these patients were women.

Table 1.

| Year  | Total number<br>of new patients | Spondylosis rhizomelica |       |
|-------|---------------------------------|-------------------------|-------|
|       |                                 | men                     | women |
| 1931  | 2823                            | 10                      | 1     |
| 1932  | 2620                            |                         |       |
| 1933  | 2577                            |                         |       |
| 1934  | 2702                            | 10                      | 3     |
| 1935  | 3203                            | 15                      | 1     |
| 1936  | 3372                            | 16                      | 1     |
| 1937  | 2394                            | 16                      | 1     |
| 1938  | 2434                            | 17                      | 0     |
| 1939  | 2527                            | 11                      | 3     |
| 1940  | 2379                            | 15                      | 0     |
| Total | 27031                           | 110                     | 10    |

After the foregoing it will be clear that most of these patients came to us without a correct diagnosis had been made. Many of them had been suffering from their disease already during many years. Although this can be readily understood, it has been a regrettable fact as especially at the beginning of the anomaly much good can be done for these patients in order to prevent invalidity.

It is not my intention to go at this place further into the difficulties of early recognition. In the literature, also from Dutch side, this has been done extensively [Krebs (4), Scott (5), Fischer-Vontz (6), Forestier (7), Tempelaar (8), Touw (9), Kuypers (10), Vos (11), Herzberger (12) etc.] When we meet the following symptoms: persistent pains of sciatic nature, irradiating to the legs, some times also to the arms, which do not react soon to induced treatment, a bad general condition, much sweating, a limitation of the functions of the spine, for the detection of which the patient must be examined without any clothes and with good illumination; a limited thoracic breathing excursion, measured over the nipples, sometimes a skinfold across the abdomen, an acceleration of the sedimentation rate of the red blood corpuscles, and on the x-ray pictures affection of the sacro-iliac joints often combined with a slight osteoporosis, the diagnosis is clear, although the vertebral co-



lumn may be roentgenologically symptomfree (also without ossification of the ligaments and bamboo-formation.) As it is already said, in early cases the affection of the sacroiliac joints is often the only objective roentgenological symptom. It may precede the other signs by years. [Scott (5), Krebs (4), Fischer-Vontz (6), Tempelaar (8) etc.]

Meanwhile the diagnosis of the early cases remains difficult, even when all aids and appliances are at hand, and if the examiner is well aware of the syndrom. More than once it occurred to us that we treated a patient during many years without knowing that a spondylosis rhizomelica was present, and on the other hand some times we diagnosed clinically a spondylosis whereas during the further investigation quite an other process appeared to exist.

As is generally known the greater joints, most often the shoulders and the hips, some times also the knees may be affected during the course of the disease, hence the apposition «rhizomelica». Often the affection starts with complaints about these articulations. Some times they precede the proper affection of the spine by many years. In such cases the recognition is already considerably difficult. Less generally known is the fact that also the little joints of the hands and the feet may participate. Even the disease may start as a primary chronic polyarthritis (rheumatoid arthritis) of the periferal joints, with swellings, osteoporosis of the skeleton, pains in the hands and more often in the feet with limitation of the functions etc. That in these cases one stands to great difficulties concerning the differential diagnosis between rheumatoid arthritis and spondylosis rhizomelica, is comprehensible, the more as during these phase the patients have no complaints yet about their back, and the existence of a spondylosis is not thought of at all.

Yet the distinction between these two syndroms is of the greatest therapeutic interest, as the spondylosis reacts badly or not to goldtherapy (according to the experience of others and also of us) in contrary with the rheumatoid arthritis, where this treatment shows such favourable results. Valuable time is lost some times in dealing with these extra ordinary forms of spondylosis, by giving one or more series of goldsalt injections, whereas the treatment should have been otherwise (physical therapy, exercises, x-ray treatment.)

From the examination of the literature it appears that some

authors mention the possibility of spondylosis rhizomelica and rheumatoid arthritis running hand in hand, a somewhat extensive number of cases however is seldom met with in their publications.

Thus Fischer and Vontz (6) stated that 14 % of their patients with spondylosis rhizomelica had been suffering from an acute polyarthrititis (rheumatic fever). In 29 % of their patients the disease started with »allmählichen Gelenkschwellungen». Also Lyon (13) communicates the fact that in spondylosis rhizomelica there are forms »ou l'on peut se demander si une arthrite banale ne coexiste pas avec la spondylose rhizomélique», whereas Ramond says that the disease sometimes starts »par une polyarthrite aiguë des membres.» Kienböck (14) mentions also the fact that besides the big joints, not so frequent however, the periferal joints may be affected. According to Thomson (15) »occasionally one sees a case with a history of a sudden onset of general arthritis.» Bachmann (16) found in 85 % of his patients »rheumatic» joint anomalies, this being a much higher incidence than other authors observed. Also Assmann (17) and Engel (18) described some cases.

Although it is clear that several authors observed the coincidence of a polyarthrititis of the periferal joints and spondylosis rhizomelica, the literature about it is scanty. In the Dutch literature, as far as I could ascertain, I found no publication devoted to this coincidence. Tempelaar who wrote an article about 100 cases of spondylosis rhizomelica of our consulting bureau, did not notice this coincidence in his material.

Therefore some abbreviated case histories may follow, which illustrate clearly the combination of these two syndroms, a diagnostic, therapeutic, and pathogenetic very interesting phenomenon. Every detail, not being important for the understanding of the course will be omitted in order to save space.

### Case-Histories.

**Case No. I.** Hist. Morbi. no. 1979 k. R. G. A man aged 31 years complains since his childhood days about pains of the hips, lateron also of the shoulders. During the first examination at our institute (1934) a distinct tenderness of the first lumbar vertebra is found. The shoulders and the left hip are free. The right hip shows a severely limited function. On the x-ray pictures the sacro-iliac joints appeared to be not quite normal. The sedimentation-rate was accelerated (15 mm during the first hour, 45 mm,

during the second hour according to the technique of Westergren which has been used always.) The seroreactions for syphilis fell out negative.

Although several suspect symptoms were present the diagnosis spondylosis rhizomelica could not be made with certainty. During the next years complaints about the periferal joints especially of the little joints of the feet, were prevalent. During a voyage to South Africa the patient complained much about the joints of the hands and feet. As to his complaints of the back he had been in a reasonable condition. During a reexamination at our consulting bureau rheumatoid arthritis (of infectious nature) was diagnosed. (1939) The influence of a recently surpassed gonococcic infection upon the process was thought of. Certainly this venereal infection had activated the symptoms. The left articulatio talo-cruralis and talo-calcanea was severely swollen. During treatment with vaccins, physical therapy, and goldsalt injections (1050 mgs. of solganol B. ol.) the condition failed to improve. The sedimentation rate rose to 77 mm during the first hour.

Neither did rubrophen treatment, which at first seemed to give good success (and during which the sedimentation rate sank to 26 mm during the first hour) bring lasting results.

At the end of 1940 the complaints about back-aches grew gradually worse. About the periferal joints no complaints were present anymore. The patient was sweating abundantly, he had a flat back, and a severely limited function of the spine. The other joints were symptom free at this time. On the x-ray pictures a distinct osteoporosis, affection of the sacroiliac joints, and of the little intervertebral joints were seen. The completely developed clinical picture of a spondylis rhizomelica was present. Treatment with x-ray irradiations has been started since, the condition at the present time is reasonably good.

*Epicrisis.* A man of 31 years complained since his childhood days about pains of the hips. At the first examination some symptoms are met with, which suggest the diagnosis of spondylosis rhizomelica, however no certainty concerning this diagnosis can be obtained. Lateron periferal joint manifestations become prevalent, so that the diagnosis rheumatoid arthritis is diagnosed, and a series of gold salt injections is given, which gave but little relief. After some years the complete picture of spondylosis rhizomelica is present. The symptoms have been activated by a gonococcic infection.

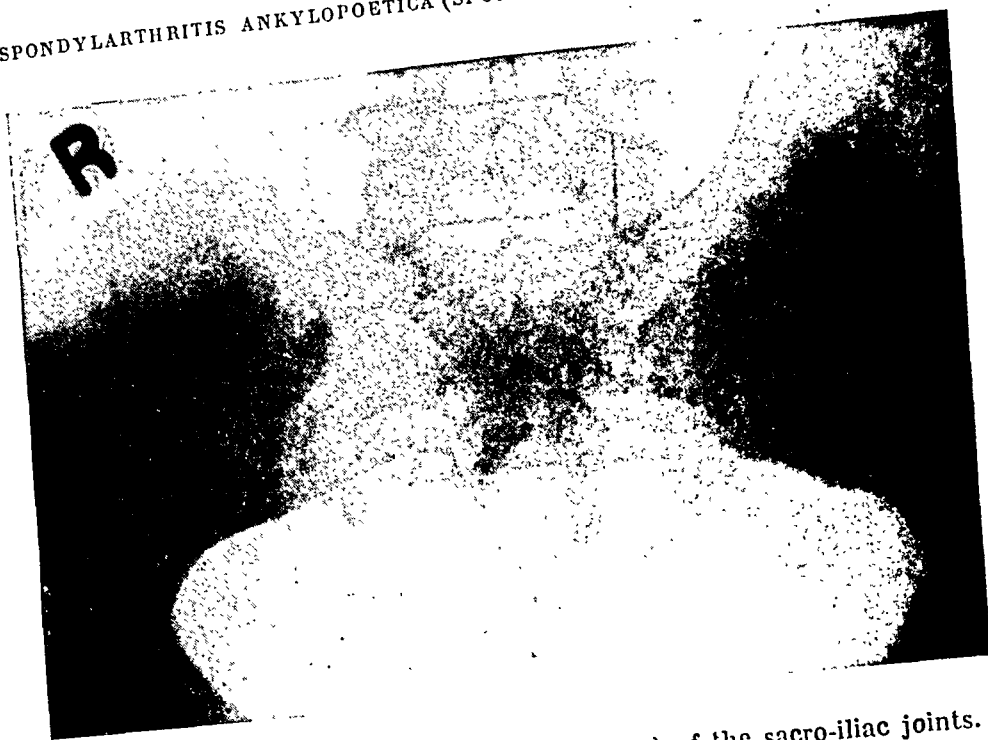
*Case No. II.* Hist. Morbi no. sp. D. M. v. D. A man of 44 years has been suffering from rheumatic fever in 1936. During this time he had already low back pains. He complained about tenderness and weakness of the knees, ankles and the interphalangeal joints of the R. thumb. We found tenderness of many little joints of the hands, of the feet, and of the

knees. The sedimentation rate came to 85 mm during the first hour. During this time he received a series of Solganal B. injections. The effect was favourable and the sedimentation rate sank to 5 mm. In 1940 he came back with many complaints. The same articulations were affected. A new course of goldsalt injections had no good effect. During this course the complaints about the shoulders, backaches and stiffness grew worse. The functions of the spine appeared to be strongly limited. A spasmus of the long muscles of the back was present. The X-ray examinations revealed affection of the sacro-iliac joints. A bony ankylosis was seen between the third and fourth lumbar vertebra. The little joints between the vertebrae were also affected. A severe osteoporosis of the columna vertebralis was present. The sedimentation rate came to 47 mm during the first hour.

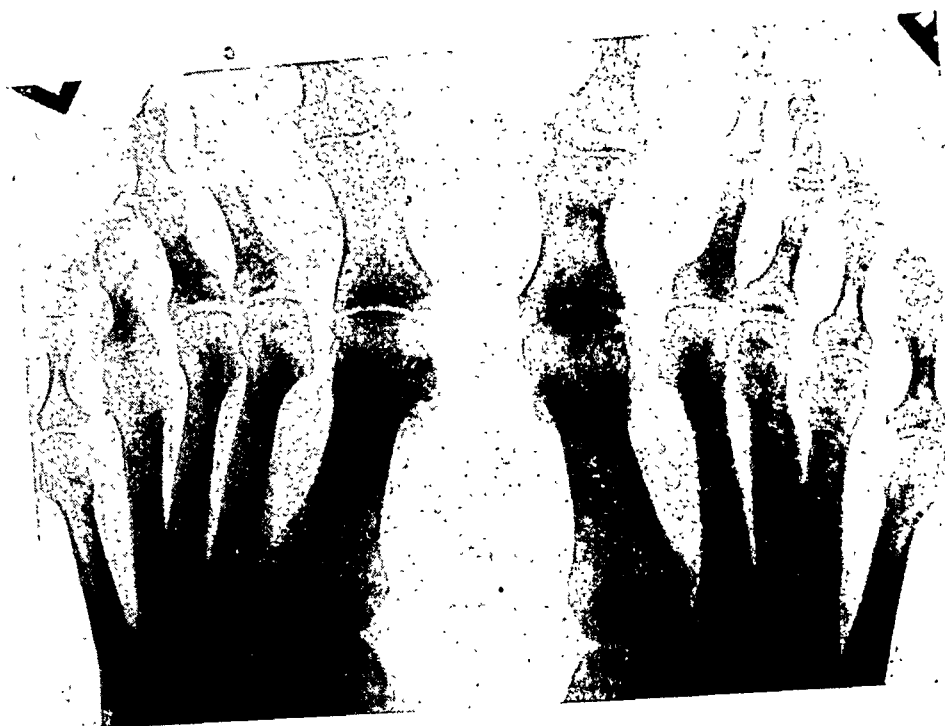
*Epicrisis.* A man of 44 years suffered from rheumatic fever. Afterwards complaints about the peripheral joints are present. They lead us to the diagnosis »subacute polyarthritis» and a series of gold salt injections was given at first with favourable effect. After some years a spondylosis rhizomelica appeared to be present.

*Case No. III.* Hist. Morbi no. 565 j. J. F. M. A man of 33 years has been suffering since 1931 from sciatica, as well from the R as from the L side, for which he was treated with physical therapy. In 1936 he got a painful swelling of the L ankle. Since 1938 he complained about his feet, back and neck. During the examination the endorotation of the R. shoulder appeared to be limited. The elbows, pulses and hands were free. The R. hip joint was somewhat limited, the metatarso-phalangeal joints showed a tenderness at motion and at pressure. Also the regio metatarsalea was tender. The sedimentation rate, which was already slightly elevated in 1934 (26 mm during the first hour) came to 68 mm in 1938. Infective arthritis (rheumatoid arthritis) was diagnosed. Goldtreatment was induced. On the X-ray pictures of the feet, slight osteoporosis was seen, around the little joints, and also disappearance of cartilage and bone destruction. The roentgenological diagnosis (Professor Dr. J. van Ebbenhorst Tengbergen) was also infective arthritis. In 1934 already an exposure of the sacro-iliac joints had been made. Although the left articulation appeared to be somewhat suspect no obvious anomaly could be discovered.

The complaints about backache grew worse during the last year. During a new examination a limited motion of the back appeared to exist. The thoracic breathing excursion was reduced, the sedimentation rate remained elevated in spite of gold treatment, the complaints did not improve. The possibility of an existing spondylosis rhizomelica was thought of. On the X-ray picture, made in March 1941 the sacro-iliac joints were affected. The vertebral column did not show obvious anomalies yet. The sedimentation rate came to 58 mm during the first hour (15 April 1941). In 1929 the patient suffered from a gonococcal infection.



Case no. III. Grave affection (disappearance) of the sacro-iliac joints.



Case no. III. Periarticular osteoporosis. Destruction of cartilage. Bone usurpation in articulation metatarso-phalangea of the L. fourth toe.



Case no. III. Periarticular osteoporosis. Destruction of the first interphalangeal joint of the fourth finger of the R. hand, with periarticular swelling.

*Epicrisis.* A man of 33 years suffered from a gonococcic infection. Some years later a bilateral sciatic syndrome developed. After 9 years he complained about several periferal joints. After clinical and roentgenological examination a rheumatoid arthritis was diagnosed. Goldtreatment was induced without favourable results. After two years a spondylosis rhizomelica in the sacro-iliac phase appeared to be present.

**Case No. IV.** Hist. Morbi no. 3170T.F. de H. A man of 54 years suffered at the age of 19 from an attack of rheumatic fever with swollen ankles, knees and hands.

During the last months of 1940 he complained again about swollen ankles. Since 4 weeks there was also a back ache. During the examination the L. shoulder and the L. hip showed a limited function. The talocrural articulations were swollen and painful, the toes were stiff, the hands showed no

anomalies. The examinations of the spine revealed a slightly limited motion. An obvious flat back existed, the thoracic breathing excursion came to 1 cm. During the further observation swellings of the interphalangeal joints of the second R finger and the third L finger appeared. The sedimentation rate came to 95 mm. The X-ray pictures showed a severe osteoporosis of the left shoulder, a disappearance of cartilage and severe osteophyt formation in the feet, osteoporosis and deviations. The hands showed »Heberdens noduli» only. On the X-ray pictures of the spine the thoracic part appeared to be normal, the 3rd, 4th and 5th lumbar vertebra showed an osteoporosis, the ligamentum interspinale showed ossification, the sacro-iliac joints had disappeared. The picture is very difficult to understand. Clinically as well as roentgenologically the condition resembles most a spondylosis rhizomelica with affection of the periferal joints, which do not show the typical signs of rheumatoid arthritis.

*Epicrisis.* A man of 54 years passes through an attack of rheumatic fever in his youth. Afterwards he is 34 years symptom free and than a spondylosis rhizomelica with affection of the big joints as well as of the little periferal joints developes.

*Case No. V.* Hist. Morb. no. 835 p. D. G. A man of 51 years came to our consulting bureau for the first time in 1937. He had been suffering from attacks of rheumatism already during 20 years. At the age of 23 he had suffered from a gonorrhoea, with a complicating gonarthritis, since then he has been suffering several times from a recurrent iritis, for the last time some weeks before the examination at our institute. He had been hospitalised for it in the university ophthalmological clinic. During some months he complained about back aches. The functions of the spine appeared to be limited in all directions. A swelling of the metacarpophalangeal joint of the second finger of the left hand was present, the right foot was tender. The x-ray picture of the hands showed periarticular osteoporosis as it is always seen in early cases of infective polyarthritis. The sedimentation rate came to 37 mm during the 1st hour. Rheumatoid arthritis was diagnosed. During the further observation the condition did not improve after physical therapy. After half a year the patient recieved a series of solganol injections. Neither this treatment gave beneficial effects. Two years later he again sought relief, this time principally because of his back aches. At the examination the limitation of the functions of the spine had become worse, a thoracic kyphosis was present, the thoracic breathing excursion measured 2 cm. The sedimentation rate came to 20 mm during the 1st. hour and the x-ray pictures of the spine showed ossification of the ligaments between the vertebrae, the sacro-iliac joints had disappeared. The completely developed picture of spondylosis rhizomelica was present.

*Epicrisis.* A man of 51 years had been suffering from a gonococcal infection in his youth, after this recurrent rheumatic sym-

ptoms remained (e. g. gonarthrititis and recurrent iritides). At the age of 48 years the clinical picture of infective polyarthrititis developed, for which gold treatment has been given, without untoward effects. Some years later a spondylosis rhizomelica is present.

**Case No. VI.** Hist. Morb. no. 53 i J. F. A man of 34 years who suffered from gonorrhoea during his youth, has been treated in 1932 for a lumbago. No further anomalies were found at that time except painful rotation of both hips. In 1936 he came again with complaints of several joints: ankles, knees, hands, pulses etc. The complaints were transient, affecting several joints in succession. He had been treated during 9 weeks in a hospital. At our examination the mobility of the shoulders was free. The right sternoclavicular joint was tender, the ellbows, pulses and hips were free, movement of the knees was painful. Both talocrural joints were tender, the left joint was swollen. Some metatarso-phalangeal joints were tender also. Subacute polyarthrititis (Rheumatic State) was diagnosed. The sedimentation rate came to 20 mm during the first hour. In 1937 a slight limitation of the function of the spine was present. Also the thoracic breathing excursion was reduced. The sign of Lassegue was present on both sides. The x-ray pictures showed no further anomalies but affection of the sacro-iliac joints. The diagnosis: spondylosis rhizomelica incipiens was clear. During the following years the patient remained in a good condition. In 1941 he again complained of back-aches. The functions of the spine remained fairly well. The thoracic excursion came to 3 cm, the sedimentation rate to 7 mm.

**Epicrisis.** A man of 34 years complained about back-ache during several weeks, which disappeared after the application of physical therapie. After 4 years he suffered from a disease which made the impression of a secondary subacute polyarthrititis. Still a year later he showed the clinical and roentgenological picture of a spondylosis rhizomelica. The disease showed hardly any progress, the patient remained in an excellent condition. During his youth he suffered from gonorrhoea.

**Case No. VII.** Hist. Morbi no. Sp. L. B. A man of 51 years came to the Consulting Bureau for the first time in 1937 with complaints of his knees, shoulders and lumbar region. The complaints existed already during 7 years. He had been hospitalised in one of the Amsterdam hospitals during 6 months. During this observation he developed a thrombosis of the R. leg. During our examination the hips were free, the R. knee was tender and it showed capsular infiltration. The functions of the spine were unlimited, but somewhat stiff. The sedimentation rate was accelerated and came to 60 mm during the first hour. The uric-acid content of the blood was raised i. e. 5.5 mg per 100 cm<sup>3</sup> of serum. Because of this fact we thought of an existing



«chronic gouty» condition. During the treatment with physical procedures (heat, diathermy, ultra-violetlight) the condition improved but the accelerated sedimentation rate persisted. During 1940 the complaints came back and he was hospitalised again in another Amsterdam hospital where a recurrent rheumatic polyarthrititis was diagnosed. He showed affections of the R. ankle and R. knee joint. Aside from this the complaints of back ache were progressive. He was treated with salicylates, cincophen, Pyramidon and heat applications. Furthermore he got some gold salt injections.

During July 1941 he came again to our policlinic. At this time the back aches were prevalent. During the examination the spine appeared to be stiff and the thoracic breathing-excursion only came to 2 cm. He had a flat back and a skinfold accross the abdomen. The sacro-iliac joints were painful, the sign of Mennell was positive. The right knee was severely swollen and painful, the hips were free, an arthritis of the R. articulatio talocruralis, the articulatio talo-calcanea, and also of the metatarso-phalangeal joint of the R. great toe.

The X-ray pictures showed affected sacro-iliac-joints, further a slight ossification between the 1st and the 2nd lumbar vertebrae. The sedimentation rate was severely accelerated, 128 mm during the first hour. The uric-acid content came to 4 mg per 100 cm<sup>3</sup> of serum (according to Kowarski's technic) Spondylosis rhizomelica had to be diagnosed at this time. Also this man had been suffering from gonococcic infection during his youth.

*Epicrisis.* A man of 51 years, who acquired a gonococcic infection in his youth, suffered since 10 years from vague rheumatic complaints with intermittent swellings of some joints, which made at first the clinical impression of chronic rheumatic polyarthrititis, which was diagnosed during two clinical observations. Four years afterwards the obvious clinical picture of spondylosis rhizomelica appeared to be present.

*Case No. VIII.* Hist. Morbi no. 1224. V.D. den O. A man of 52 years had already complaints about his back during 25 years, to which he had grown accustomed. In 1941 he searched treatment for complaints of the knees and pulse-joints, which existed for half a year. During our examination the spine appeared to be stiff in toto.

There was an obvious skinfold accross the abdomen, the respiration-excursion, measured over the nipples, was 2 cm. The R. shoulder was limited and also the R. hip; the knees and the talo-crural joints were free. The pulses were severely swollen. The function of the spine was severely limited and painful. No swellings of the interphalangeal joints. The sedimentation rate came to 57 mm during the first hour. On the X-ray pictures the cartilage of the pulses was thinned, furthermore periarticular osteoporosis; around every joint usurpation of bone was seen. Infective arthritis of hands and pulses was diagnosed. The sacro-iliac joints were affected and had near-

ly disappeared; there was bony ankylosis between the 4th and 5th lumbar vertebrae. The interspinal ligaments were ossified: spondylosis rhizomelica was present.

*Epicrisis.* A man of 52 years had been suffering already during 25 years from a spondylosis rhizomelica which had lead to total stiffness of the spine. Since half a year he showed signs of infective arthritis (rheumatoid arthritis) of the periferal joints.

*Case No. IX.* Hist. Morbi. no. 3426 S. T. S. This man of 40 years came for the first time to our consulting bureau in December 1939. Since 9 months he complained of pains of the back and of the shoulders. He could not bend. 6 Years ago he suffered from «sciatica». His father suffered from rheumatism, his brother who is known at our bureau suffers also from spondylosis rhizomelica. Some months ago he acquired a gonorrhoea for which hospitalisation was necessary.

His spine appeared to be stiff, only the cervical part could make moderate movements. The thoracic breathing excursion measured 2.5 cm. The movements of the hips were slightly limited, the knees were not free. The sedimentation rate came to 18 mm during the first, 45 mm during the second hour. On the x-ray pictures the sacro-iliac joints were affected, and had nearly disappeared. Ossification of the lateral ligaments between the lumbar vertebrae was present.

The patient did not come for further treatment. In December 1941 he came again. He told us that his complaints had gradually disappeared, and that he had been symptomfree. In May 1941 he had acquired a new gonococcic urethritis, for which again hospitalisation had been necessary. Aside from his complaints of the back, which have returned since some months, he complains of swollen hands and feet. During the examination the knees appear to be swollen, crepitation and limitation of function are present. Furthermore there is an arthritis of the right talocrural joint, with swelling and painful limited motion, also some metacarpo-phalangeal joints are swollen and painful. The sedimentation-rate comes to 13 mm. during the first hour.

*Epicrisis.* A man of 40 years suffered from sciatica. After six years he acquired a gonococcic infection, at the same time he complains of back-aches. A spondylosis rhizomelica appears to be present. He did not come back for further treatment. Two years later he acquired again a gonococcic infection. Aside from his spondylosis rhizomelica periferal arthritis of several joints is observed, the complaints have become worse after, and probably in connection with the gonococcic infection.

His father suffers from «rheumatism», his brother from spondylosis rhizomelica.

### Comment.

In the cases of spondylosis rhizomelica, all occurring in men, described above, the recognition of the condition has given many difficulties so that 6 of these patients were known to us already during resp. 6, 4, 10, 2, 5 and 4 years without the exact diagnosis had been evaluated at our institute. Two of these patients even had been clinically observed in other hospitals during many months. The attending physicians had not the slightest suspect of the true underlying condition. This remarkable fact must be principally ascribed to the atypical, often very slowly progressing course of the disease during its first phase. Indeed the anomalies of the peripheral joints were prevalent during a longstanding period in such a way that in most of these cases primary or secondary chronic polyarthritis had been diagnosed, without the existence of a spondylosis rhizomelica had been thought of. The treatment in these cases has been instituted accordingly (goldtreatment in 6 patients) without beneficial results, another point of accordance of these cases.

The question whether we are dealing here with two separate conditions, coinciding in one patient i. e. spondylosis rhizomelica (spondylarthrosis ankylopoetica) and chronic polyarthritis (rheumatoid arthritis) or whether the whole syndrom has to be considered as one morbid entity arises in thinking these cases over. An answer to this question can not be given until it is settled where to place the spondylosis rhizomelica amongst the rheumatic conditions.

Whereas Pierre Marie and Leri (19) at first were of opinion that spondylosis rhizomelica was an »ostéopathie«, we know nowadays that this disease must be considered to be an arthritis of the articulations between the vertebrae; an inflammation probably starting from the sacroiliac joints. Already Strümpell (20) drew attention to the relation of »Rheumatismus« and spondylosis rhizomelica, and accepted the infectious nature of the affection. Wehrsig (21) who reported the literature until 1910 mentioned the fact that 40 % of the cases had a »rheumatic« etiology. Most of the modern authors consider the spondylosis to be an infectious condition, equivalent to the rheumatoid arthritis (chronic polyarthritis); they consider it to be the »rheumatoid arthritis of the spine« [Prochster (22) 1924, Assmann (17) 1929, Fischer-Vontz (6) 1932, Teschendorf (23) 1933,

Burchhardt (24) 1934, Strebel (25) 1935, Francon (26) 1936, Kienböck (13, 27, 28) 1938, Edström (29) 1940].

Indeed many clinical and pathological facts plead for this conception. Both the affections show a syndrom which makes the clinical impression of a chronic infection (slight elevation of the body temperature, profuse sweating, emaciation, bad general condition, slight toxic symptoms of the leucocyte formula, accelerated sedimentation rate of the red blood corpuscles etc.), both syndroms occur almost during the same age period (30—50 years), run an extreme chronic course, affect many joints, and at last become inactive.

Yet there are many points of controverse: The almost exclusive occurrence of spondylosis rhizomelica in men, whereas chronic progressive polyarthritis is seen more often in women; the limitation of the process in spondylosis rhizomelica to the stem, whereas in primary chronic polyarthritis the periferal joints, nearly always are affected symmetrically; the prevalent ossification of the ligaments in spondylosis rhizomelica, whereas this phenomenon in rheumatoid arthritis is never met with (or extremely seldom), and finally the excellent reaction of chronic polyarthritis to goldtreatment, whereas spondylosis rhizomelica mosttimes does not show any good influence from this form of treatment. The reasons of the different behaviour and predilection of these two syndroms can only be guessed, a definite explanation cannot be given as long as more fundamental knowledge about the true nature of these affections is lacking. Perhaps it is connected with the difference between the functions of the spine and the periferal articulations of the extremities, the former to support and carry the trunk, the latter to secure the movements of the body (legs) and to carry out all the functions needed in daily life (arms and hands). It is easy to understand that the difference in function of those two joint-systems may influence the course of the affecting diseases. Probably the cause of the different behaviour and predilection of the two syndroms is also connected with a difference in ontogenetic development, between the spine, and the periferal joints. It would be of interest to go further into these questions but it is not my intention to do so at this place.

Meanwhile Gamna (30) does not agree with these theoretical considerations and considers the spondylosis to be an autonomous

disease, characterised by decalcification of the vertebrae and »syndesmophytosis» of the ligaments, caused by infectious agents.

It goes without saying that, as it was generally accepted that spondylosis rhizomelica is an infectious condition (a conception which has not yet been proved, according to Fischer-Vontz) many authors wondered which of the well-known pathogenetic micro-organisms had to be held responsible for the syndrom. A specific infection with well-known causative microbes can not be taken in consideration according to Fischer-Vontz. The gonococcus and the treponema pallidum are not accepted as causative agents, in spite of the fact that gonorrhoea and syphilis occurred resp. in 11 % and 7 % of their cases. Strebel (25) who mentions true rheumatism (echter Rheumatismus) to be the etiological factor, describes a case where to his account the gonococcus had to be regarded as the »true» cause of the rheumatism (i. e. the spondylosis rhizomelica) and the complicating iritis. Perhaps this is also true for our case no. V where also the gonococcus might have played an important rôle. Lyon (13) is of opinion that sometimes gonorrhoea, seldom tuberculosis, and in exceptional cases syphilis may be of etiological importance.

Forestier's (7) opinion is that genital infections (gonorrhoea) play a very important rôle. He explains the nearly exclusive occurrence of spondylosis in men from anatomical dispositions, typical for the masculin sex. The lymphvessels of the prostatic gland and the vesiculae seminales run to the praesacral glands and from here the lymph runs along the spine upwards, forming many anastomoses with the sacro-iliac- and vertebral plexus. In women only the lymphvessels of the uterus follow this way, those from the eustachian tubes and the ovariae run to the iliac glands and after this to the praecoeliac chain.

Also the tubercle bacillus was often considered to be the true cause of spondylosis rhizomelica. According to Fischer-Vontz unjustly. Only in 3 % of their material (100 cases) tuberculosis was manifest. Diametrically opposed to theirs and nearly isolated stands the opinion of Kienböck, who considers in nearly all cases the tubercle bacillus as the only cause of the disease, thus considering this affection to be a manifestation of tuberculosis. The same applies to the acute rheumatic polyarthrititis (rheumatic fever) as well as to the primary chronic progressive symmetrical polyarthrititis (rheumatoid arthritis). Thus Kienböck enlargens the opinion of Grocco-Poncet;

he became convinced of the exactness of his theory by roentgenological evidences (often slight tuberculous lesions in the lungs and in the bones e. g. os ischium, os pubis, tibia etc.), the often occurrence of tuberculous abscesses in patients suffering from the above mentioned diseases, the clinical symptoms, and by a few findings at autopsies and at operations, where the tubercle bacillus could be directly demonstrated in the tissues.

In spondylosis rhizomelica, to his opinion the primary lesion should be localized in the urogenital system, the spread of the infection taking place along the lymphatic system. He considers the spondylosis to be an «exsudative synostosing form» («exsudativ-synostosierende Form») of joint tuberculosis.

Although his conception is very disputable, and he himself gives no extensive casuistic documentation, his description of some cases, i. e. of a case in which chronic progressive polyarthrititis and spondylosis rhizomelica developed in consequence of a tuberculous lesion of the right tibia, is very remarkable. The great merit of this conception is the fact that Kienböck regards the many different «rheumatic» conditions from one point of view, they all being different manifestations of essentially one infection. In connection with this the experiments of Reiter-Löwenstein (31) may be incidentally reminded. These authors thought to have cultured tubercle bacilli from the blood of sufferers from rheumatic fever. Later on it appeared that the results of these experiments were unreliable, and could not be reproduced by others (e. g. Fischer).

Meanwhile the infectious nature of spondylosis rhizomelica is not yet proved. Also endocrine factors have been considered to be of etiologic importance. The opinion of Oppell who held a hyperfunction of the parathyreoid glands responsible for the outbreak of spondylosis has been abandoned at the present time. However sometimes improvement of the condition has been noticed after parathyreoid-ectomy, especially by French investigators (Lyon). Lemmertz and Köddermann (32) accepted hypofunction of the testes and of the pituitary gland as an important etiologic factor. They consider the affection as a «hormonal dyscrasia» and saw clinical improvement in a number of cases after the application of testosterone propionate and hormones of the anterior lobe of the pituitary. The often occurrence of sterility in marriages of spondylosis patients plead for this conception.

How it is, for the present time the words of Ramond: »Quant à la nature de ces arthrites vertébrales, elles nous est encore inconnue, comme nous est inconnue celle du rhumatisme chronique en général» appears to be true.

In connection with these words it is perhaps not superfluous to condemn the faulty standpoint, too much held by some authors, that a certain microorganism can be the true and only cause of spondylosis rhizomelica. As it is so often put forward by van Breemen and others, we must be well aware of the fact, that for the development of a rheumatic affection, such as spondylosis rhizomelica (as it is the case for the development of any other disease e. g. ulcer of the stomach, cancer, cirrhosis of the liver, tuberculosis, hay-fever etc. etc.) many factors are important: endogenous factors (constitution of the patient, heredity, sex, age, endocrine conditions, neurovegetative disturbances, anomalies of the blood circulation etc.) and exogenous factors (such as climate, occupation of the patient, social welfare, intoxications, civilisation habits, infectious agents etc.) The infectious microorganisms form also only one, truly sometimes very important, part of the complex of factors which provoke the morbid condition.

Our own cases do not give clear etiological indications either. Truly it is a remarkable fact that 6 from these 9 patients suffered from gonorrhoea (no's 1, 3, 5, 6, 7, 9). In four of these patients the rheumatic complaints started in connection with this infection, or were aggravated by it, a fact which is very typically demonstrated in case record no 5. This patient acquired a gonococcic urethritis 28 years ago, in consequence of this he suffered from a complicating gonarthrititis, and thereafter from repeated iritides. In 1937 he showed a clinical syndrom which made the impression of a rheumatoid arthritis and two years afterwards he had a spondylosis rhizomelica. But also the cases no. 1, no. 3 and no. 9 make a connection between the gonococcic infection, the rheumatic polyarthrititis and the spondylosis rhizomelica very acceptable.

Furthermore two patients have suffered from rheumatic fever, and one from a subacute polyarthrititis, some time before the spondylosis developed.

As it is seen there are curious anamnestic data in the case histories of these 9 patients in abundance, without a straight etiologic line can be traced, the number of patients being too small for this.

Nevertheless these cases give, to my opinion a clear indication to the hypothesis that an intimate connection has to be accepted between rheumatoid arthritis and spondylois rhizomelica, whatever the underlying cause of the affections may be.

To my opinion these two clinical pictures must be considered as one morbid entity. Also this is true for case no. 8 which showed a clinical course different from the others: here the spondylosis existed during 25 years before the symptoms of periferal arthritis appeared.

Although we have theoretically to do with one morbid entity, most of our patients show either the syndrom of rheumatoid arthritis, or of spondylosis alone. The combination is very seldom seen, as it appears from our figures (nearly 7 % of our spondylosis patients showing the combination with periferal arthritis). It remains of practical and therapeutic interest not to overlook this periferal arthritis in treating a patient who suffers from spondylosis, and even of greater importance not to overlook the spondylosis when it is present in a patient who is treated for rheumatoid arthritis.

Concerning the diagnosis the advice cannot be given with too much strength to examine the spine also in patients suffering from acute or chronic polyarthritis, especially when the patient complains of low back pain, a fact which is relatively often present. In cases of doubt the roentgenological examination of the sacro-iliac joints and of the spine may not be omitted. The more this applies to patients who are treated with goldsalt injections because of an existing rheumatoid arthritis, and who do not improve, whereas the sedimentation-rate does not show the intention to fall. In such cases the possibility of an existing spondylosis in combination with the rheumatoid arthritis must be kept in mind. Probably in doing so it can be avoided that these patients visit their doctors during many years without their spondylosis being recognised, and may an earlier induced treatment prevent invalidity.

That x-ray treatment of the spine and the sacroiliac joints must not be delayed in these cases goes without saying, especially since we know from the publications of Altschul (33), Grabowsky (34), Haenisch (35), Kemén (36), Quartero (37), Smith, Freyberg, Peck (38) and from our own experience (39) that this form of treatment in combination with physical therapy (ultraviolet light, heat applications, exercises etc.) is of the most effective in combatting this affection.



### Summary.

After a brief discussion on the difficulties concerning the evaluation of the diagnosis in cases of spondylosis rhizomelica at the beginning of its development, the author communicates the fact that amongst 27031 patients suffering from rheumatic illness, who visited the Amsterdam consulting bureau since 1931, 120 cases of spondylosis occurred; 10 of these belonged to the female sex. 9 Case histories are described briefly, because they all showed a combination of spondylosis rhizomelica and periferal polyarthrititis, making the clinical impression of rheumatoid arthritis, a relatively seldom occurrence, which made the evaluation of the diagnosis very difficult, so that many of these cases were known during many years without the exact diagnosis had been made.

The author puts forward his opinion that these two syndroms must be considered to form one morbid entity. Some brief remarks concerning the diagnosis and the etiology are made, and stress is laid on the necessity not to overlook an existing spondylosis in patients suffering from rheumatoid arthritis, especially when they do not react well to goldtreatment.

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From the Medical Department of the Chr. Michelsen Institute, Bergen,  
Norway.

(Chief: Konrad Birkhaug, M. Sc., M. D.)

## Hematology in experimental Tuberculosis.

The Hemogram in Anaphylactic-Allergic and Anaphylactic-Iatrogenic  
Tuberculous Guinea Pigs.

By

KONRAD BIRKHAUG and HALFDAN SCHJELDERUP.

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In a series of investigations on immunity in experimental tuberculosis, the senior author has made an earnest attempt during the past decade to clarify the part played by bacterial allergy in resistance in tuberculosis (1), an issue upon which opinion is seriously divided. One group of investigators regards bacterial allergy in tuberculosis as a beneficent and protective mechanism, the result of which is a vigorous attack upon the fresh microbic invader and its rapid destruction (2). Another group considers bacterial allergy in tuberculosis a merely incidental and mainly harmful accident which bears no necessary relation to true immunity (3). It is not our wish in this place to embark upon a general discussion of bacterial allergy in tuberculosis, which has been masterly done by Arnold R. Rich and Howard McCordock (4), and cursorily done by the senior author on several occasions (5). We shall only briefly recapitulate some salient results of our own experiments which support the proposition that *allergy is not necessary for the operation of immunity in tuberculosis*.

Our first step was to immunize and sensitize guinea pigs by a subcutaneous injection of the avirulent BCG-culture mixed with mol-

ten paraffin. This procedure immunizes and allergizes more effectively and durably than the usual parenteral injection of the BCG-culture alone. A proportion of these animals was subsequently desensitized (rendered *iathergic-immune*) by thrice weekly doses of tuberculin, sufficiently small to prevent development of pulmonary congestion, encountered by Willis and Woodruff (6), and yet large enough to maintain a negative tuberculin reaction in the skin. Both groups of animals were then superinfected with virulent tubercle bacilli and desensitization was continued by thrice weekly doses of tuberculin in the *iathergic* group. Since absolute immunity to virulent tubercle bacilli is impossible of accomplishment in the guinea pig, the effects of such proceedings can only be considered relatively. The visceral tuberculous hyperplasia was, therefore, measured volumetrically and the distribution of viable tubercle bacilli was determined by culture of exact weights of viscera. These quantitative data were finally compared with those obtained in the normal controls, and the total results were evaluated statistically. The normal controls showed the most extensive and rapidly fulminating visceral tuberculous lesions, heavily laden with viable tubercle bacilli. The allergic animals showed a moderate reduction in the extent and bacillary content of the tuberculous lesions. The desensitized *iathergic* immune animals showed a nearly complete protection. In other words, abolishing the allergic condition so far from diminishing resistance, had increased it. This confirmed the adroit phrase coined by S. Lyle Cummins (7) that «allergy is the shadow but not the substance of immunity in tuberculosis.» Believing bacterial allergy and true immunity to constitute independent and separable biological phenomena, one of us postulated that a specific allergen and immunogen were responsible for the production of tissue inflammation and necrosis on the one hand and resistance to infection on the other hand. The isolation of chemically pure allergen and immunogen would undoubtedly find considerable theoretical and practical importance. Such a pure immunogen might possibly render vaccination with living avirulent tubercle bacilli (B. C. G.) unnecessary for the protection against tuberculous infection, without the tuberculin reaction becoming positive as a result of immunization. This latter fact complicates the epidemiological surveys for open cases of tuberculosis which mainly depends on a negative tuberculin test suddenly turning positive as a result of

spontaneous infection. The problem of isolation of chemically pure allergen and immunogen has recently been considerably advanced by chemical fractionations of the tubercle bacilli conducted by Widström (8) at the Physical-Chemical Institute at the Uppsala University. He has made a preliminary statement to the effect that the isolated allergen sensitizes without conferring any immunity while the immunogen immunizes without sensitizing the organism.

In order further to clarify the part played by bacterial allergy in resistance in tuberculosis, we have resorted to hematology as an *intra vitam* presumptive test of the status of visceral tuberculous lesions inaccessible to direct biopsy (9). We have already shown in guinea pigs primarily infected with virulent tubercle bacilli that certain blood cells and cellular ratios deviate with constancy in upward or downward direction from the normal base-line and always in direct progression with advancing tuberculous disease. Such deviations are slightly inhibited in the allergic immune animals and nearly completely eliminated in the desensitized iathergic immune animals. This we accept as further proof that bacterial allergy is unessential for the full function of resistance to infection. Thus the happy combination of bacteriology, pathology and hematology has yielded results which permit the supposition that bacterial allergy and true immunity are separate biological phenomena whose concurrent presence in tuberculosis is merely accidental.

This differential investigation was carried one step farther by our recent separation of anaphylaxis, allergy and immunity in tuberculosis (10). Even as we had succeeded to abolish bacterial allergy by desensitization with tuberculin, without removing immunity, we had also separated bacterial anaphylaxis from bacterial allergy. The crucial proof of the separability of concurrent anaphylaxis, allergy and immunity in one and the same guinea pig organism was accomplished, so far as is known to us, for the very first time in our last publication in this series (11). It would thus appear that the antigens contained within the tubercle bacillus are as complex as those in other bacteria and that at least three of these, namely anaphylactogen, allergen and immunogen, are capable of producing differentiable and specific biological reactions. The present paper deals with the hematology in the tuberculo-anaphylactic-allergic and iathergic immune animals employed in our recent (11) publication.

*Materials and methods.*

We shall briefly connect these hematological investigations with the experimental procedures published previously (11). Thirty-six normal guinea pigs weighing on the average 550 gms were employed. The experiment commenced August 12th and terminated December 15th 1941. The animals were divided into three equal groups. Groups I (iathergic immune) and II (allergic immune) were sensitized anaphylactically by the injection into the exposed jugular vein of 1.92 mg purified BCG tuberculoprotein contained in 2 cm<sup>3</sup> of saline adjusted with ammonia to pH 7.2. Group III (normal controls) were not sensitized anaphylactically. The day after the anaphylactic sensitization, groups I and II were injected in the left thigh muscles, for the purpose of allergization and immunization, with 200 mg semi-dried BCG mixed with 1 cm<sup>3</sup> molten paraffin (M. P. 54° C). This mass hardened immediately *in situ*. When the experiment was terminated approximately 130 days later, the BCG-paraffin focus had been retained intact by 66.7 percent in group I and 33.3 percent in group II. We have previously (1940) described the greater tolerance of the iathergic immune animals than the allergic immune animals for the paraffin BCG focus and this partly accounts for the nearly complete protection in the former animals. It is recalled that Lurie (12) has shown that in the presence of sufficient residual primary lesions, the bacilli of reinfection are quickly destroyed without preliminary multiplication. Group I animals were desensitized by thrice weekly subcutaneous injections of 100 mg tuberculin. Desensitization commenced the day after the injection of the BCG-paraffin focus. Desensitization was controlled weekly by intracutaneous injection of 10 mg tuberculin. Desensitization was complete in 75 percent up till 6 weeks after the commencement of the experiment when the desensitizing dose was increased to 200 mg until the experiment was terminated 10 weeks later. Two-three animals remained recalcitrant to complete desensitization, but their cutaneous reactions of erythema and infiltration were insignificantly small. All group II animals became strongly allergic and the difference in volumetric infiltration in the skin 48 hours after the intracutaneous injection of 10 mg tuberculin from that in group I was approximately 16 times greater than their standard error.

Two months after the anaphylactic sensitization and the injection of the BCG-paraffin focus, all the animals in groups I and II, as well as group III normal controls, were injected *intraperitoneally* with 0.005 mg (approximately 37,000 viable) virulent human tubercle bacilli. The intraperitoneal test infection is a far greater tax on the acquired tuberculo-immunity than the usual subcutaneous inoculation. Hence the resistance offered by any one group of animals is a more crucial test of the rôle played by the presence or absence of bacterial allergy than if the subcutaneous route of inoculation had been chosen. Desensitization of group I was continued with about the same results as discussed above. The experiment was terminated 4 months after its commencement. During this time group I had lost only 1/15th of the original body weight, group II had lost 1/7th and group III as much as 1/3d. Two group III animals died 50 and 54 days after the virulent inoculation from fulminating tuberculosis. These two animals presented such advanced visceral lesions, which could readily be measured volumetrically, that it was decided to terminate the experiment whose purpose was an attempt to demonstrate and to separate the concurrent states of tuberculo-anaphylaxis, allergy and immunity.

The thirty-four surviving animals were sacrificed between the 55th and 65th post-inoculation days in the following manner: 6 iathergic immune group I animals were killed by acute anaphylactic shock (bronchospastic asphyxia) 4—5 minutes after the intravenous injection of the specific anaphylactogen. The remaining 6 animals in this group survived the slow intravenous injection of the specific anaphylactogen and after having become anti-anaphylactic, they remained well without succumbing from the lethal dose of tuberculin contained in the tuberculoprotein anaphylactogen. This proof of complete desensitization should be remembered by those who contend that complete desensitization is impossible of accomplishment. All the animals in group I were found at autopsy to be completely or nearly completely protected against the virulent inoculation and 1 g of splenic tissue contained on the average 975 viable tubercle bacilli which were held in check without producing macroscopic tuberculous lesions. Six animals in group II (allergic immune) died in acute anaphylactic shock after the intravenous injection of the specific anaphylactogen. The remaining 6 animals in this group survived the slow injection of the anaphylactogen, but

died 10—12 hours later from profound allergic intoxication. All these animals presented moderately advanced generalized tuberculosis and 1 g of splenic tissue contained on the average 62,112 viable tubercle bacilli. The surviving 10 allergic-control group III animals, which had neither been sensitized anaphylactically nor rendered allergic or immune before the virulent inoculation, died in protracted tuberculin intoxication after the intravenous injection of the tuberculo-protein anaphylactogen. All these animals presented advanced visceral tuberculosis and 1 g of the spleen contained on the average 99,221 viable tubercle bacilli.

Thus, tuberculo-anaphylaxis, allergy and immunity have been produced concurrently and separated as characteristic and apparently unrelated biological phenomena in one and the same animal organism. Tuberculo-anaphylaxis appears to exert no influence on the allergic or iathergic (immune) conditions and spontaneous anaphylaxis is a remote possibility in tuberculosis. Bacterial allergy produces inflammation and necrosis in tuberculous lesions and increases the multiplication and spreading of tubercle bacilli. Limitation and healing are associated with low tissue sensitivity and high resistance.

The hematological investigation was made on eighteen animals, six from each of the three groups. In the iathergic immune group we employed only completely desensitized animals. The normal base-lines for hemoglobin, erythrocytes and leukocytes, differential cells and cellular ratios were made on the basis of 180 individual pre-inoculation counts, i. e. before the virulent superinfection took place. The assessment of the weekly deviations was not done on the basis of a common normal value, but on the basis of the pre-inoculation values obtained in each particular group. Counts were made on the 11th, 17th, 24th, 33d, 38th, 45th, 52d and 58 days after the virulent superinfection.

The hemoglobin determinations were done with the OKA hemoglobinometre constructed on the Sahli principle with a glass standard substituted for the acid hematin liquid standard of the original Sahli. The glass standard represents 16 gms of hemoglobin per 100 cm<sup>3</sup> of blood. Enumeration of the total red and white blood cells were done according to the Ellermann dilution principle, making use of standardized separate pipettes for blood and diluting fluids and the mixture taking place in special diluting



tubes. In this manner one may count the cells immediately or later. Standardized green glass Levy quadruple counting chambers were employed for the blood counts. As a routine, we counted 200 small squares for erythrocytes and ten large squares (each one square millimeter) for total leukocytes. The blood smears were fixed in absolute alcohol for 5 minutes, dried and stained with the Romanowsky-Giemsa stain. One hundred differential cells were counted by each of the authors in each smear and whenever two counts showed excessive divergence, the counts were repeated, at times up to 600 cells.

The hematological data for each group of animals were treated separately and always compared with the base-line values for that group. As in our previous work, Fisher's (13) statistics were employed to determine whether two samples differed significantly in their mean or whether they should be regarded as belonging to the same population. The pre-inoculation counts done on each animal group served as specific controls. The subsequent weekly post-inoculation counts in each group were treated together by weeks. The mean standard deviation and probable error of the mean value were determined in each animal group for the hemoglobin, the total red and white blood cells, the differential cells and the cellular ratios, at each time interval, i. e. on the 11th, 17th, 24th . . . etc. post-inoculation periods. The significance of deviations in the various blood cells or cellular ratios was determined by calculating the deviations from the base-line mean and by determining the probable error of this deviation and dividing the former by the latter. This *t* quotient expresses the deviation as a multiple of its probable error. The statistical significance (*P* or probability) of various values of such quotients was taken from Fisher and Yates (14) table III. From this table it may be seen that deviations having a  $t = 3.169$  occur by chance only once in 100 times. Therefore, the value  $t = 3.169$  was taken as the limit for normal variation; and deviations of order greater than this have a probability of 100 to 1, or more, of being significant. Deviations of lesser order were considered not to be of certain significance. The shaded areas in charts 1 to 7 show the magnitude only beyond which deviations of the mean counts of individual blood cells or cellular ratios were considered to be of undisputed significance.

Values for the absolute number of erythrocytes and leukocytes

were employed while the percentages of differential blood cells were used inasmuch as these represent more exactly the proportions of weekly deviations from the base-line value than their absolute number obtained by converting the percentage into an absolute number. Were the values of total leukocytes constant during the post-inoculation time intervals, rather than as in our case highly fluctuating, then one might employ the calculated absolute numbers rather than the actually counted percentages of differential blood cells. In order to demonstrate the discrepancy which may arise from converting obtained percentages into calculated absolute numbers when the numbers of total leukocytes show appreciable fluctuations, we have in Table 2 contrasted the percentage of eosinophiles against the calculated absolute numbers of these cells in our three groups of animals. We observe that no significant deviations occur in any one group when the percentage values serve as basis of calculation. On the contrary, we obtain respectively 37.5 percent significant deviations in group I, and 12.5 percent in each of groups II and III when the same percentages are converted into calculated numbers of eosinophiles. Without making use of statistical analysis, it is quite apparent that no significant deviations were present to allow for such percentages.

The hematological study included 180 pre-inoculation counts and 480 post-inoculation counts. Each group of animals was represented by the same counts at each time interval and the mean values represented six counts. The monocyte-lymphocyte ratio employed was proposed by Cunningham, Sabin, Sugiyama and Kindwall (15), the neutrophile-lymphocyte ratio by Crawford (16) and the leukocytic index by Crawford and Medlar (17). Instead of employing the »Arneth index» (18) which divides the neutrophiles into five groups according to their nuclear lobulation, we have made use of Schilling's (19) simplified »index» which has become an indispensable method of clinical and pathological investigation. This author divides the neutrophilic cells into myelocytes, with kidney- or oval-shaped nucleus, which never appear in the normal circulating blood; juvenile cells, with sausage- or bean-shaped nucleus with nucleoli, which normally is absent; stab or staff cells with narrow or bandlike nucleus which contain no nucleoli and appear in 2 to 4 percent in the blood stream; the adult or segmented neutrophile which make up about 63 percent of the normal human white cell

count. In performing the ordinary differential count of leukocytes, each of these types is counted separately, so that, in the complete result, each variety of neutrophilic granular cell is expressed as a percentage of the total number of leukocytes, while in the Arneth »index» they are expressed only as a percentage of the total neutrophilic cells. It should be pointed out at once that the »hemogram» in the normal guinea pig varies slightly from that of the human and in Table I we observe that it is as follows: erythrocytes,  $5,262,000 \pm 140,600$ , hemoglobin, 94.5 percent  $\pm 1.26$ , leukocytes,  $9,560 \pm 1,028$ , eosinophiles, 4.66 percent  $\pm 0.28$ , basophiles, 1.08 percent  $\pm 0.94$ , lymphocytes, 44.17 percent  $\pm 4.47$ , monocytes, 4.50 percent  $\pm 2.52$ , myelocytes, nil, juveniles, 0.67 percent  $\pm 0.42$ , stab cells, 4.50 percent  $\pm 2.53$  and segmented cells, 40.41 percent  $\pm 3.29$ .

#### *Hematological results.*

*Hemoglobin:* During the entire post-inoculation period we observed no significant deviation in the hemoglobin percentages from the pre-inoculation base-line in the desensitized group I animals. The average post-inoculation percentage was 95.50 in this group. In the allergic group II animals the hemoglobin percentage fell significantly low 45 and 58 days after inoculation when it registered respectively 85.17 and 66.00 percent, with an average post-inoculation percentage of 83.77. In the control group III animals we observed the most rapid and excessive fall, commencing already 33 days after inoculation to become significant with 80 percent hemoglobin and terminating at 56 percent during the last determination. The average post-inoculation record was 77.7 percent hemoglobin in this group. As an indicator of the influence of a virulent tuberculous infection on the hemoglobin percentage we find no significant deviations in the desensitized animals, 50 percent significant deviations in the allergic animals and 75 percent in the controls. (Table 1 and Chart 1).

*Red blood cells:* In the desensitized group I animals we observed a significant increment in red blood cells 45 days after inoculation to 5,942,000 from a base-line of 5,245,000 and this tendency continued to 6,223,000 cells 58 days after inoculation. This enhanced erythropoiesis in the presence of a virulent tuberculous inocu-

Table

Mean ante-inoculation and mean post-inoculation values for differential blood allergic-control guinea pigs inoculated in-

|                                    | Animal groups | Base-line<br>10-X-1941 |              |              |
|------------------------------------|---------------|------------------------|--------------|--------------|
|                                    |               |                        | 11<br>(21-X) | 17<br>(27-X) |
| Hemoglobin .....                   | 1             | 95.30                  |              | 96.80        |
|                                    | 2             | 94.70                  |              | 95.70        |
|                                    | 3             | 94.50                  |              | 95.30        |
| Red blood cells .....              | 1             | 5,245                  |              | 5,398        |
|                                    | 2             | 5,362                  |              | 5,403        |
|                                    | 3             | 5,262                  |              | 5,030        |
| White blood cells .....            | 1             | 15,000                 | 14,628       | 10,478       |
|                                    | 2             | 18,670                 | 20,633       | 23,893       |
|                                    | 3             | 9,560                  | 22,727       | 18,633       |
| Juvenile cells .....               | 1             | 0.67                   | 0.90         | 0.30         |
|                                    | 2             | 0.67                   | 0.70         | 0.40         |
|                                    | 3             | 0.67                   | 0.80         | 0.50         |
| Stab cells .....                   | 1             | 3.75                   | 3.30         | 3.80         |
|                                    | 2             | 3.00                   | 2.90         | 2.30         |
|                                    | 3             | 4.50                   | 3.60         | 3.80         |
| Segmented cells .....              | 1             | 48.09                  | 39.30        | 51.30        |
|                                    | 2             | 39.42                  | 43.10        | 39.30        |
|                                    | 3             | 40.41                  | 33.80        | 32.40        |
| Neutrophiles .....                 | 1             | 53.00                  | 43.50        | 55.50        |
|                                    | 2             | 43.00                  | 46.70        | 40.90        |
|                                    | 3             | 46.25                  | 38.20        | 36.70        |
| Basophiles .....                   | 1             | 1.58                   | 0.80         | 0.80         |
|                                    | 2             | 0.33                   | 0.40         | 0.50         |
|                                    | 3             | 1.08                   | 0.70         | 1.00         |
| Eosinophiles .....                 | 1             | 4.83                   | 6.70         | 6.80         |
|                                    | 2             | 4.66                   | 3.80         | 3.80         |
|                                    | 3             | 4.66                   | 11.30        | 9.60         |
| Lymphocytes .....                  | 1             | 35.50                  | 43.30        | 34.50        |
|                                    | 2             | 45.25                  | 43.30        | 48.90        |
|                                    | 3             | 44.17                  | 46.30        | 43.40        |
| Monocytes .....                    | 1             | 5.58                   | 4.80         | 5.90         |
|                                    | 2             | 6.67                   | 6.00         | 5.60         |
|                                    | 3             | 4.50                   | 3.60         | 9.20         |
| Leukocytic index .....             | 1             | 20.5                   | 13.0         | 16.7         |
|                                    | 2             | 15.5                   | 19.8         | 15.3         |
|                                    | 3             | 2.7                    | 17.6         | 16.3         |
| Monocyte-lymphocyte ratio .....    | 1             | 0.161                  | 0.112        | 0.189        |
|                                    | 2             | 0.149                  | 0.094        | 0.124        |
|                                    | 3             | 0.106                  | 0.080        | 0.205        |
| Neutrophile-lymphocyte ratio ..... | 1             | 1.531                  | 0.514        | 1.730        |
|                                    | 2             | 0.963                  | 1.101        | 0.701        |
|                                    | 3             | 1.046                  | 0.911        | 0.844        |

Note: Statistically significant deviations from the pre-inoculation base-line significant deviations from the pre-inoculation base-line.

<sup>1</sup> The significant deviations were in the direction of an increase from the allergic-control group which were in the direction of a decrease.

<sup>2</sup> The significant deviations were in the direction of a decrease from the allergic-control group which were in the direction of an increase.

1.

cells and cellular ratios in (1) iatrogenic-immune, (2) allergic-immune, and (3) intraperitoneally with virulent tubercle bacilli.

| Post-inoculation days |               |               |               |               |               | Post-inoculation  |   |
|-----------------------|---------------|---------------|---------------|---------------|---------------|-------------------|---|
| 24<br>(3-XI)          | 33<br>(12-XI) | 38<br>(17-XI) | 45<br>(24-XI) | 52<br>(1-XII) | 58<br>(8-XII) | Average<br>values | Efficiencies of<br>deviations from<br>base-line<br>per cent |
|                       | 96.70         |               | 96.33         |               | 92.16         | 95.50             | 0   |
|                       | 88.20         |               | <i>85.17</i>  |               | <i>66.00</i>  | 83.77             | 50.0  |
|                       | <i>80.00</i>  |               | <i>79.50</i>  |               | <i>56.00</i>  | 77.70             | 75.0  |
|                       | 5,346         |               | <i>5,942</i>  |               | <i>6,223</i>  | 5,727             | (50.0) <sup>1</sup>   |
|                       | 4,812         |               | <i>4,000</i>  |               | <i>4,122</i>  | 4,584             | 50.0  |
|                       | <i>4,243</i>  |               | <i>3,682</i>  |               | <i>3,545</i>  | 4,125             | 75.0  |
| 12,606                | <i>10,007</i> | <i>10,173</i> | <i>9,800</i>  | 12,250        | 13,394        | 11,667            | (50.0) <sup>2</sup>   |
| 21,233                | 17,347        | <i>13,773</i> | 16,590        | 17,100        | <i>10,006</i> | 17,571            | (25.0) <sup>2</sup>   |
| <i>18,066</i>         | <i>14,847</i> | <i>13,766</i> | 17,187        | 14,160        | 10,846        | 16,280            | 62.5  |
| 0.30                  | 0.20          | 0.40          | 0.30          | 1.20          | 0.20          | 0.56              | 0   |
| 0.30                  | 1.10          | 0.30          | 0.20          | 0.90          | 0.80          | 0.48              | 0   |
| 0.20                  | 0.20          | 0.70          | 0.40          | 0.30          | 2.20          | 0.74              | 0   |
| 4.96                  | 3.10          | 3.80          | 4.00          | 3.30          | 2.30          | 3.57              | 0   |
| 4.20                  | 5.00          | 4.40          | 4.80          | <i>6.70</i>   | <i>6.60</i>   | 4.61              | 25.0  |
| 3.30                  | 5.30          | 4.80          | 5.40          | <i>6.70</i>   | <i>8.00</i>   | 5.11              | 25.0  |
| 49.30                 | 50.80         | 50.80         | 52.70         | 44.30         | 49.90         | 48.56             | (12.5) <sup>2</sup>   |
| 46.40                 | 37.90         | 40.80         | 49.80         | 51.90         | 54.00         | 45.40             | 0   |
| 38.90                 | 40.50         | <i>49.90</i>  | <i>50.20</i>  | <i>54.70</i>  | 46.30         | 43.34             | 37.5  |
| 54.50                 | 54.10         | 55.00         | 57.00         | 48.80         | 52.40         | 52.60             | (12.5) <sup>2</sup>   |
| 51.00                 | 44.00         | 45.50         | 54.80         | <i>59.50</i>  | <i>61.40</i>  | 50.48             | 25.0  |
| 42.50                 | 48.00         | <i>54.90</i>  | <i>56.30</i>  | <i>61.80</i>  | 54.60         | 49.12             | 50.0  |
| 1.20                  | 1.10          | 1.20          | 1.20          | 0.30          | 1.60          | 1.03              | 0   |
| 0.50                  | 0.60          | 0.40          | 0.30          | 0.90          | 0.60          | 0.53              | 0   |
| 0.60                  | 0.70          | 1.00          | 0.60          | 0.80          | 2.30          | 0.96              | 0   |
| 3.60                  | 2.40          | 4.60          | 3.00          | 6.30          | 3.40          | 4.60              | 0   |
| 1.80                  | 2.10          | 2.30          | 1.20          | 0.70          | 1.20          | 2.11              | 0   |
| 1.20                  | 5.00          | 3.30          | 2.70          | 2.30          | 4.40          | 5.35              | 0   |
| 35.70                 | 36.90         | 34.80         | 31.50         | 38.90         | 34.60         | 36.28             | 0   |
| <i>36.60</i>          | 40.00         | <i>32.60</i>  | <i>29.40</i>  | <i>22.90</i>  | <i>19.30</i>  | 34.11             | 62.5  |
| 41.50                 | <i>34.40</i>  | <i>25.00</i>  | <i>26.50</i>  | <i>16.60</i>  | <i>19.00</i>  | 31.59             | 62.5  |
| 5.00                  | 5.50          | 4.50          | 7.30          | 5.80          | 8.10          | 5.86              | 0   |
| 10.50                 | <i>13.30</i>  | <i>19.30</i>  | <i>14.20</i>  | <i>16.00</i>  | <i>17.50</i>  | 12.80             | 62.5  |
| <i>11.30</i>          | <i>11.90</i>  | <i>15.90</i>  | <i>14.20</i>  | <i>18.50</i>  | <i>19.80</i>  | 13.05             | 87.5  |
| 16.8                  | 13.0          | 14.5          | 17.5          | 18.3          | 24.1          | 16.7              | 0   |
| 26.3                  | 26.8          | <i>34.3</i>   | 38.7          | <i>52.0</i>   | <i>55.1</i>   | 33.5              | 75.0  |
| 23.0                  | 22.5          | <i>41.3</i>   | 43.0          | <i>65.0</i>   | <i>50.6</i>   | 34.9              | 100.0   |
| 0.140                 | 0.159         | 0.143         | 0.234         | 0.153         | <i>0.245</i>  | 0.172             | 12.5  |
| <i>0.291</i>          | <i>0.340</i>  | <i>0.637</i>  | <i>0.506</i>  | <i>0.761</i>  | <i>1.082</i>  | 0.479             | 75.0  |
| <i>0.282</i>          | <i>0.354</i>  | <i>0.668</i>  | <i>0.599</i>  | <i>2.642</i>  | <i>1.148</i>  | 0.747             | 87.5  |
| 1.534                 | 1.579         | 1.751         | 1.959         | 1.300         | 1.940         | 1.538             | (12.5) <sup>2</sup>   |
| 1.433                 | 1.170         | 1.558         | 2.083         | <i>3.109</i>  | <i>3.923</i>  | 1.885             | 25.0  |
| 1.103                 | 1.450         | <i>2.320</i>  | <i>2.429</i>  | <i>12.092</i> | <i>3.280</i>  | 3.054             | 50.0  |

appear in italics. Values shown in ordinary type proved not to be statistically pre-inoculation base-line and thus differ from the significant deviations in the pre-inoculation base-line and thus differ from the significant deviations in the

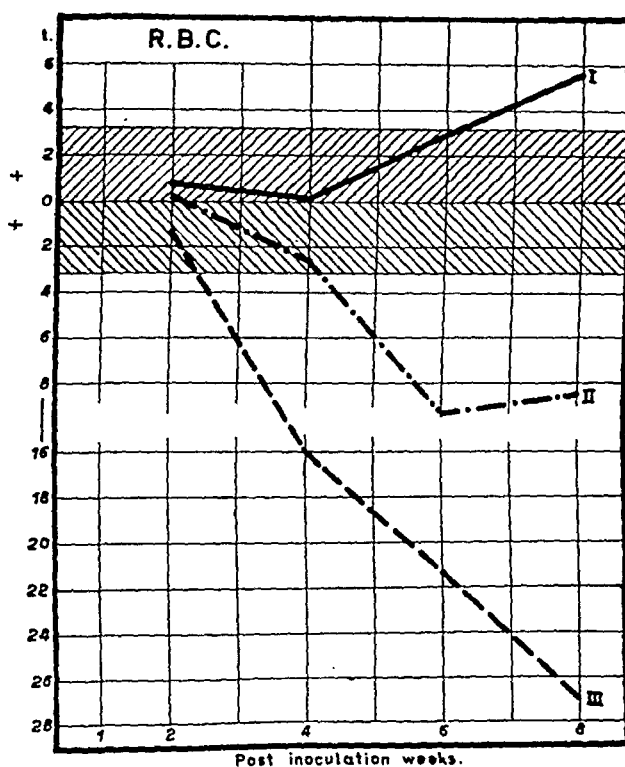
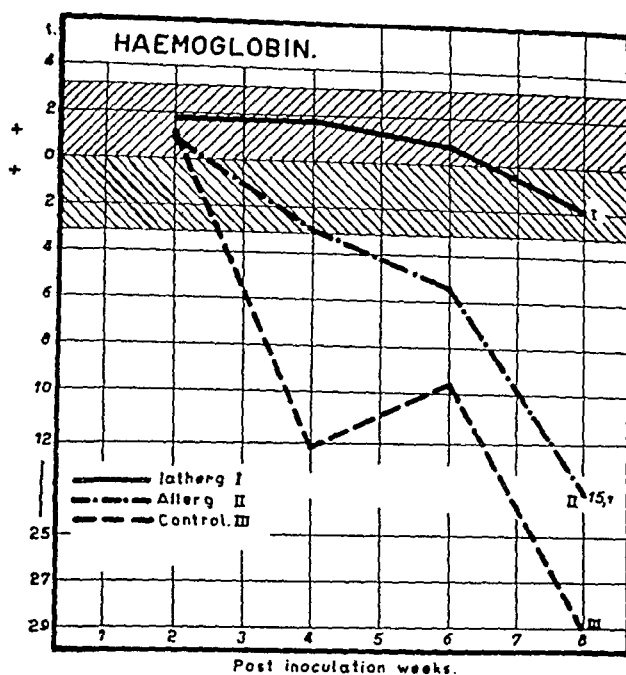


Chart 1.

Weekly mean deviations of blood constituents expressed as multiples of their probable error. The horizontal line in the centre of the shaded zone represents the normal value; the direction of each deviation from the normal is shown. Deviations falling outside the shaded area are considered significant.

lum suggested a high degree of tuberculo-resistance. In the allergic group II animals we observed a fall in the red blood cells concomitant with that of hemoglobin. The count had fallen to 4 million cells 45 days after inoculation and ended on 4,122,000 cells when the last reading was made 58 days after inoculation. While the post-inoculation average values were 5,727,000 red blood cells per cubic millimetre in the desensitized animals, they were only 4,584,000 in the allergic animals. In the control group III animals the destruction of red blood cells proceeded most rapidly and 45 days after inoculation we found only 3,682,000 cells per cubic millimetre. During the last reading 58 days after inoculation the fall had continued downwards to 3,545,000 red blood cells. The post-inoculation average for this group was 4,125,000 red blood cells per cubic millimetre. The influence of the virulent tuberculous infection on the red blood cells were therefore commensurate with that on the haemoglobin in the three groups of animals: the desensitized animals resisted any attack on the erythropoietic system while the allergic animals showed 50 percent significant downward deviations from the base-line and the control animals as much as 75 percent.

*White blood cells:* The excessive leukocytosis observed in the base-lines in the desensitized and allergic animals in groups I and II were referable to the foreign body inflammatory reaction around the BCG-paraffin focus in the left thigh, coupled with the thrice weekly injections of tuberculin in the desensitized animals. The leukocytosis in the desensitized animals abated during the post-inoculation period and nearly attained to normal limits, having a post-inoculation average of 11,667 white blood cells per cubic millimetre. Thus four of eight post-inoculation average counts were significantly lower than the base-line. It should be emphasized that 66.7 percent of the desensitized animals retained the BCG-paraffin focus intact throughout the entire infection while all of the six animals employed for the blood work had their vaccination focus intact. It is apparent, therefore, that the symbiotic equilibrium between the desensitized tissue and the BCG-paraffin focus had become a part of the acquired resistance against tubercle bacilli. In the allergic animals employed in the blood work, only one retained the BCG-paraffin focus throughout the entire post-inoculation period while the remaining 5 animals had ejected the vaccination focus during the first post-inoculation month. Nevertheless, the leu-

kocytic curve remained elevated and showed only two significantly low excursions 38 and 58 days after inoculation. Inasmuch as the tuberculous lesions in the viscera had become quite advanced 58 days after inoculation, we were inclined to ascribe this final leukopenia to the phase described by Sabin, Doan and Cunningham (20) which occur in animals presenting the more virulent progress of tuberculosis. The post-inoculation average value was 17,571 white blood cells per cubic millimetre in the allergic animals. The control animals in group III represented the leukocytic response to the intraperitoneal inoculation with virulent tubercle bacilli in the absence of any pre-inoculation manipulations. As soon as 11 days after inoculation we found a hyperleukocytosis of 22,727 cells per cubic millimetre and the subsequent counts were considerably higher than the pre-inoculation base-line. The very last count 58 days after inoculation fell down to 10,846 cells per cubic millimetre. But the average post-inoculation value was 16,280 cells. While both the desensitized and allergic leukocytic counts showed respectively 50 and 25 percent significant deviations in a downward direction from the base-lines, the control animals showed 62.5 percent significant deviation in an upward direction from the base-line, which is the true picture of leukocytosis during a virulent tuberculous infection (Table 1 and Chart 2).

*Juvenile cells:* The young metamyelocytes (with only the slightest indentation of the nucleus) showed not the slightest deviation from the base-lines in any one of the three groups of animals during the entire post-inoculation period.

*Stab cells:* The stab cells or band forms of metamyelocytes (with deep indentation, but no true lobulation of the nucleus) appeared to be uninfluenced in numbers by the virulent tuberculous infection in the desensitized group I animals during the entire post-inoculation period. In both the allergic and control animals, these older forms of metamyelocytes increased to significant numbers during the 52 and 58 post-inoculation day counts, but none of these deviations were of a high order.

*Segmented cells:* deviations from the base-line of the segmented polymorphonuclear cells were insignificant in both the desensitized and allergic animals during the post-inoculation period. In the control animals, however, we observed three significant deviations



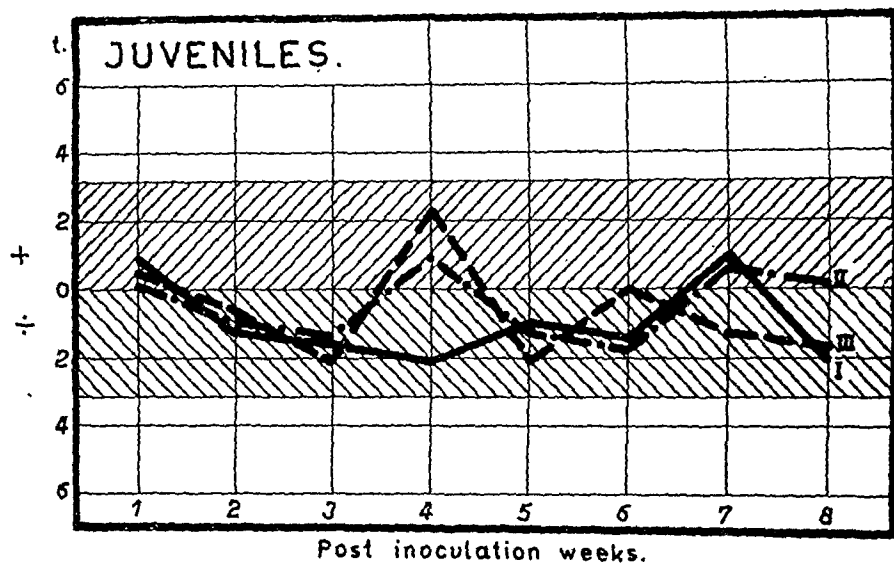
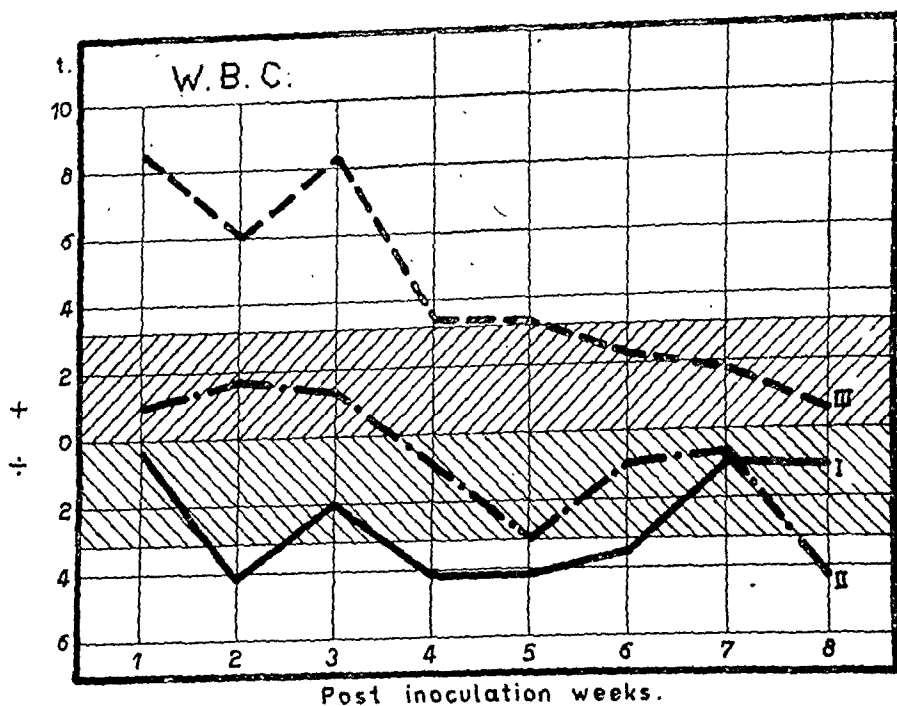


Chart 2.

during the 38th, 45th and 52nd post-inoculation counts, but as with the stab cells these deviations were not of a high order.

The use of the Schilling »hemogram» leaves the impression that this »index» is less sensitive than the Arneth »index» as an indicator of advancing tuberculous disease, or as Arneth expressed it »as a prognostic index of resistance in tuberculosis.» It is recalled that in our previous experience (1942) we found the Arneth »index»

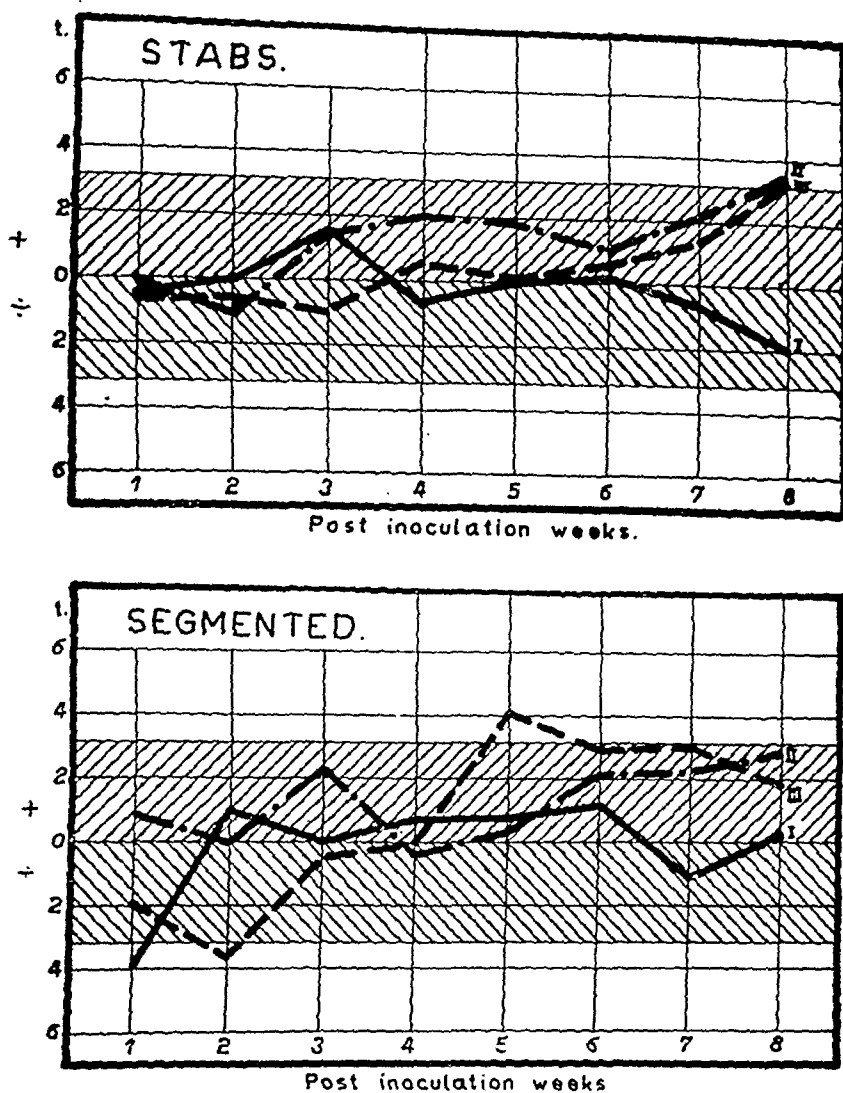


Chart 3.

closely approaching in sensitivity the efficiency of the monocyte-lymphocyte ratio and the monocyte percentage and that it was more sensitive than the neutrophile-lymphocyte ratio.

*Neutrophiles:* The level of percentages of neutrophiles was found to be nearly evenly sustained in the desensitized animals during the entire post-inoculation period and showed an average of 52.60 percent. In both the allergic and control animals we observed a decided tendency of increase in neutrophiles as the experiment drew to an end. In the allergic group II we found the base-line percentage to be 43.00 and it rose gradually to 54.80 during the 45th

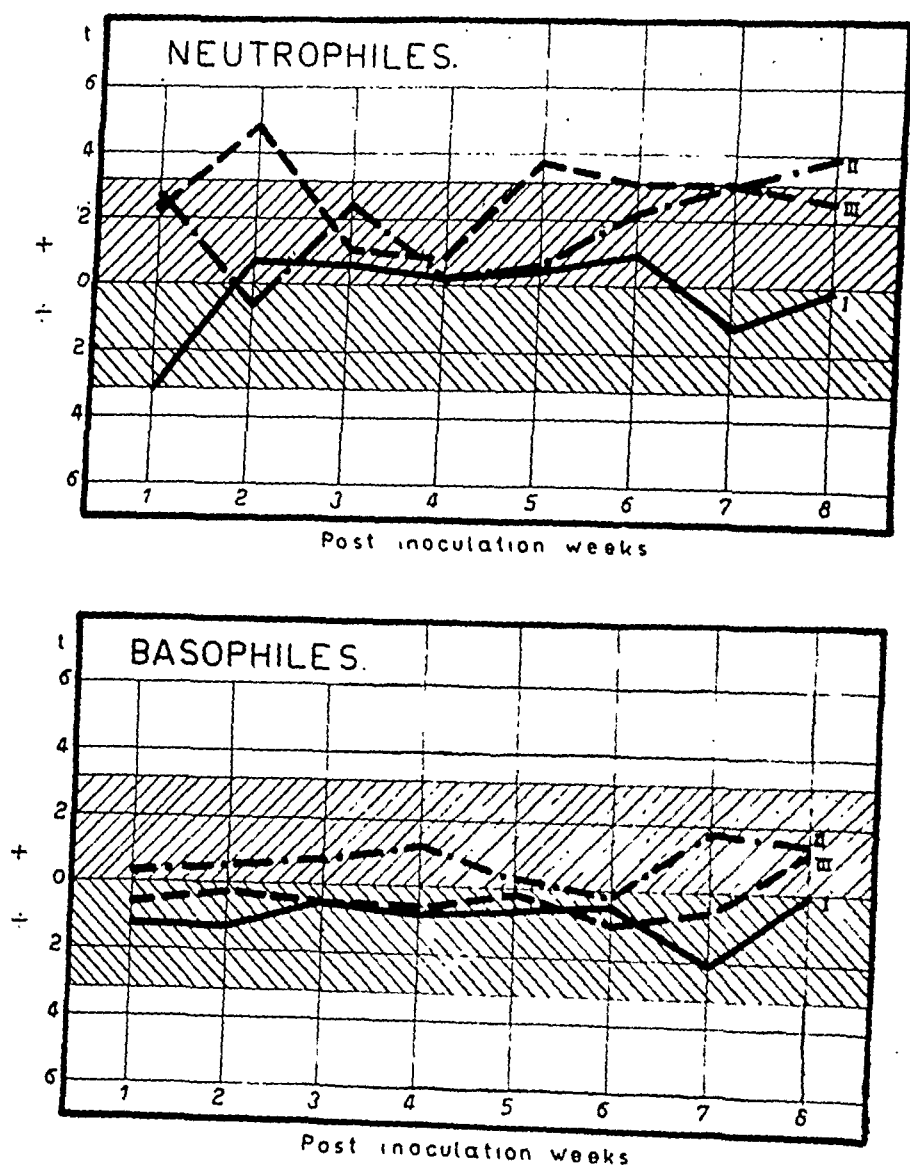


Chart 4.

post-inoculation day count and terminated at 61.40 on the 58th day. The same tendency was still more pronounced in the control group III animals. Of the eight post-inoculation counts in the allergic group two were significant, giving an efficiency of 25 percent while in the control group four were significant, one below and three above the base-line, so that the efficiency was 50 percent.

*Basophiles:* None of the three groups of animals exhibited abnormal values for basophiles during the entire post-inoculation period. Smithburn, Sabin and Hummel (21) found likewise in

rabbits no significant change in basophiles when the animals were inoculated with the most virulent cultures of tubercle bacilli.

*Eosinophiles:* As in our previous experience we observed no significant deviations from the base-line of eosinophiles in any one of the three groups of animals during the entire post-inoculation period. In the allergic group we observed a tendency to gradual disappearance of eosinophiles as the disease progressed and after the initial increments of eosinophiles in the control group, the same tendency was noticeable also in this group. But none of these

Table 2.

*Post-inoculation deviations based upon actually counted percentages of eosinophiles.*

(M = averages, T = multiples of their probable error, P = probability of being significant.)

| Animal groups  | Base-line<br>10-X-1941 | Post-inoculation days |       |       |       |       |       |       |       | Post-inoculation  |   |
|--|------------------------|-----------------------|-------|-------|-------|-------|-------|-------|-------|-------------------|---|
|  |                        | 21-X                  | 27-X  | 3-XI  | 12-XI | 17-XI | 24-XI | 1-XII | 8-XII | Average<br>values | Efficiencies of<br>deviations<br>from base-<br>line % |
| 1  | M = 4.83               | 6.70                  | 6.80  | 3.60  | 2.40  | 4.60  | 3.00  | 6.30  | 3.40  | 4.60              | 0   |
|  | T = ....               | 2.254                 | 1.055 | 0.962 | 2.559 | 2.242 | 2.098 | 0.977 | 1.444 | 2.11              |   |
|  | P = ....               | 0.05                  | 0.30  | 0.35  | 0.04  | 0.05  | 0.08  | 0.35  | 0.15  |                   |   |
| 2  | M = 4.66               | 3.80                  | 3.80  | 1.80  | 2.10  | 2.30  | 1.20  | 0.70  | 1.20  |                   | 5.35  |
|  | T = ....               | 0.488                 | 0.546 | 1.917 | 1.577 | 1.493 | 2.367 | 2.849 | 2.379 |                   |   |
|  | P = ....               | 0.65                  | 0.60  | 0.10  | 0.15  | 0.15  | 0.05  | 0.02  | 0.04  |                   |   |
| 3  | M = 4.66               | 11.30                 | 9.60  | 4.20  | 5.00  | 3.30  | 2.70  | 2.30  | 4.40  | 0.85              | 0   |
|  | T = ....               | 2.519                 | 2.015 | 0.231 | 0.216 | 0.432 | 1.416 | 1.646 | 0.151 |                   |   |
|  | P = ....               | 0.04                  | 0.07  | 0.85  | 0.85  | 0.65  | 0.20  | 0.15  | 0.85  |                   |   |
| <i>Above percentages converted into calculated absolute numbers of eosinophiles.</i><br>(According to procedure of Smithburn, Sabin and Hummel, Amer. rev. tuberc.,<br>1937, 36, 673.) |                        |                       |       |       |       |       |       |       |       |                   |   |
| 1  | M = 719                | 1003                  | 335   | 447   | 254   | 485   | 315   | 900   | 453   | 524               | 37.5  |
|  | T = ....               | 2.076                 | 3.047 | 1.435 | 3.754 | 1.633 | 3.097 | 0.626 | 1.736 | 399               |   |
|  | P = ....               | 0.05                  | 0.015 | 0.15  | 0.01  | 0.15  | 0.015 | 0.55  | 0.12  |                   |   |
| 2  | M = 895                | 784                   | 938   | 370   | 338   | 320   | 170   | 97    | 175   |                   | 974   |
|  | T = ....               | 0.315                 | 0.126 | 1.838 | 1.929 | 2.034 | 2.733 | 3.010 | 2.623 |                   |   |
|  | P = ....               | 0.72                  | 0.90  | 0.10  | 0.08  | 0.06  | 0.02  | 0.015 | 0.03  |                   |   |
| 3  | M = 470                | 2606                  | 1792  | 797   | 870   | 458   | 488   | 327   | 454   | 0.40              | 12.5  |
|  | T = ....               | 3.956                 | 2.735 | 0.924 | 1.886 | 0.554 | 0.881 | 0.809 | 0.874 |                   |   |
|  | P = ....               | 0.01                  | 0.02  | 0.34  | 0.09  | 0.60  | 0.40  | 0.42  | 0.40  |                   |   |

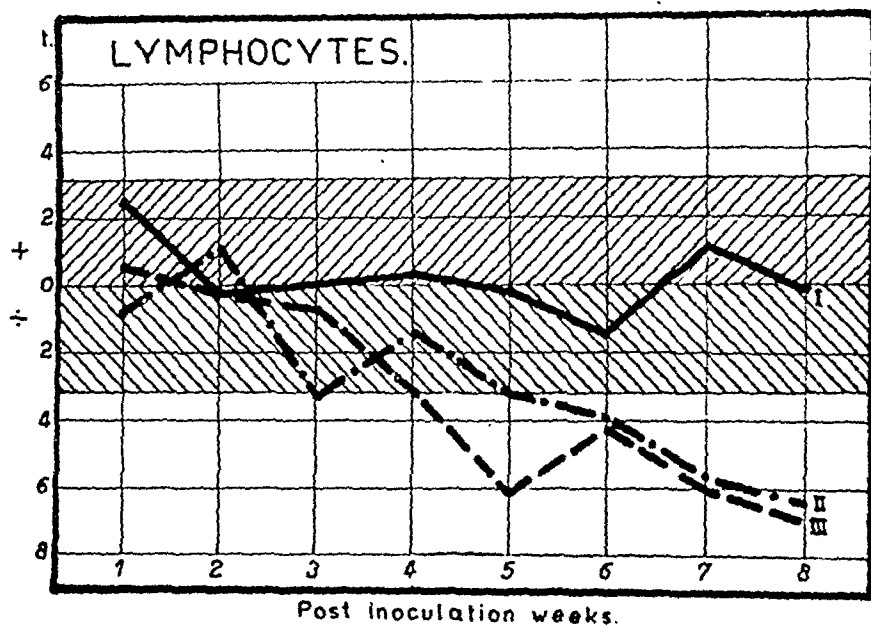
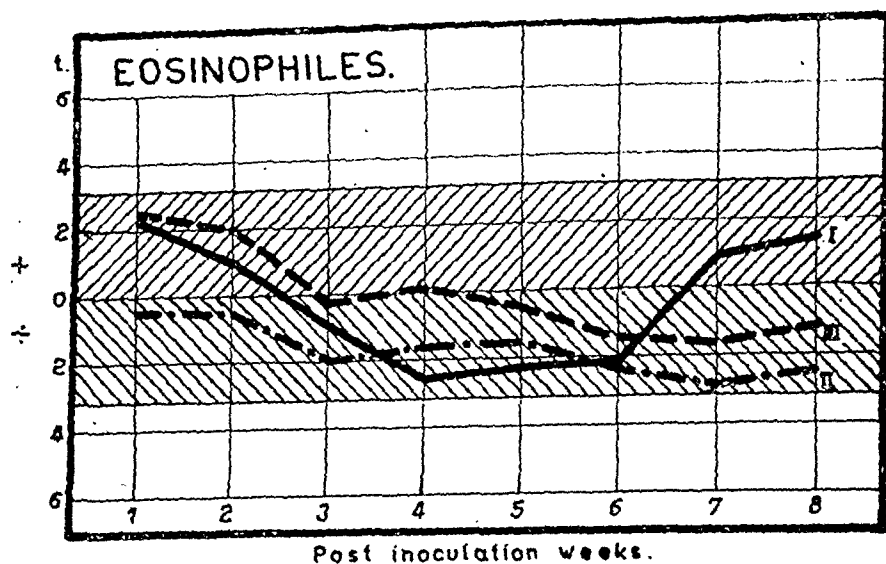


Chart 5.

downward deviations attained anywhere within significant proportions. The greater declining significant results reported by Smithburn, Sabin and Hummel (21) are possibly due to the conversion of the counted percentages of eosinophiles into actual numbers while the total leukocytic counts fluctuate at every reading. We have attempted to disclose such discrepancy in Table 2.

*Lymphocytes:* The desensitized animals in group I exhibited no abnormal values for lymphocytes during the entire post-inoculation

period. In both the allergic and control groups significant declines in circulating lymphocytes occurred respectively during the 24th day and 33d day counts and the lymphopenia persisted significantly low in each group throughout the disease. Thus, five out of eight post-inoculation values for lymphocytes in each of these two groups were significantly low, giving an efficiency of 62.5 percent for these cells in the allergic and control animals.

*Monocytes:* No significant deviations from the base-line of monocytes were observed in the desensitized group I animals during the post-inoculation period. The base-line value of 5.58 percent of monocytes had risen to only 8.10 percent during the last week of the experiment, giving a post-inoculation average of 5.86 percent of monocytes. In the allergic group II animals the base-line of 6.67 percent of monocytes became elevated to 10.50 percent during the 24th post-inoculation day and thereafter rose significantly in every subsequent count until it reached 17.50 percent. The post-inoculation average of monocytes was 12.80 percent in the allergic group and five of the eight mean post-inoculation counts for monocytes were significantly high, giving an efficiency of 62.5 percent. In the control group III all but the first post-inoculation mean values were significantly elevated from 4.50 to 19.80 percent of monocytes. The average post-inoculation value was 13.05 percent of monocytes in the control group and seven of the eight mean values for monocytes following inoculation were significantly elevated, giving an efficiency of 87.5 percent. The course of the tuberculous disease was thus reflected most accurately by these cells in our three groups of animals (Table 1 and Chart 6).

*Leukocytic index:* According to Crawford and Medlar (17) who proposed the leukocytic index, they stated that this index «equals the value of the neutrophile-lymphocyte percentage ratio plus the value of the elevation of the monocytes plus the value of the abnormal total white cell count.» On the basis of extensive clinical studies, Medlar (17) attaches the following prognostic interpretation to the leukocytic index: »0 to 15 = ideal increasing favourable; 16 to 20 = slightly favourable; 21 to 26 = slightly unfavourable; 27 to 35 = unfavourable, and 36 and over = increasingly very unfavourable.» We have on several occasions (1937, 1939, 1941 and 1942) in experimental tuberculosis confirmed Medlar's conclusion that »the leukocytic index does indicate the trend of the underlying pathological process.»

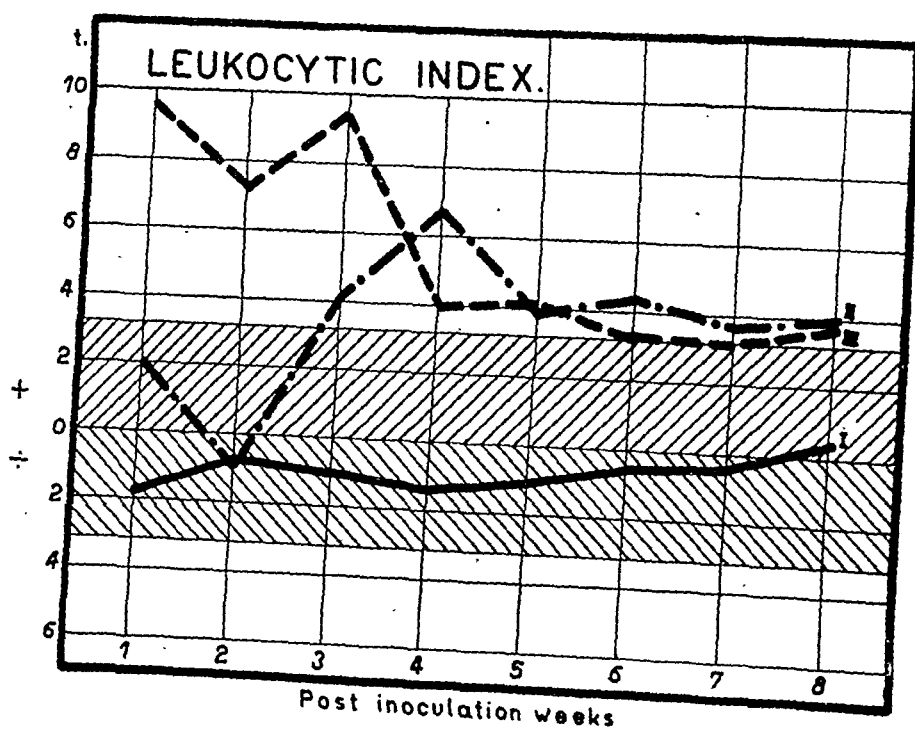
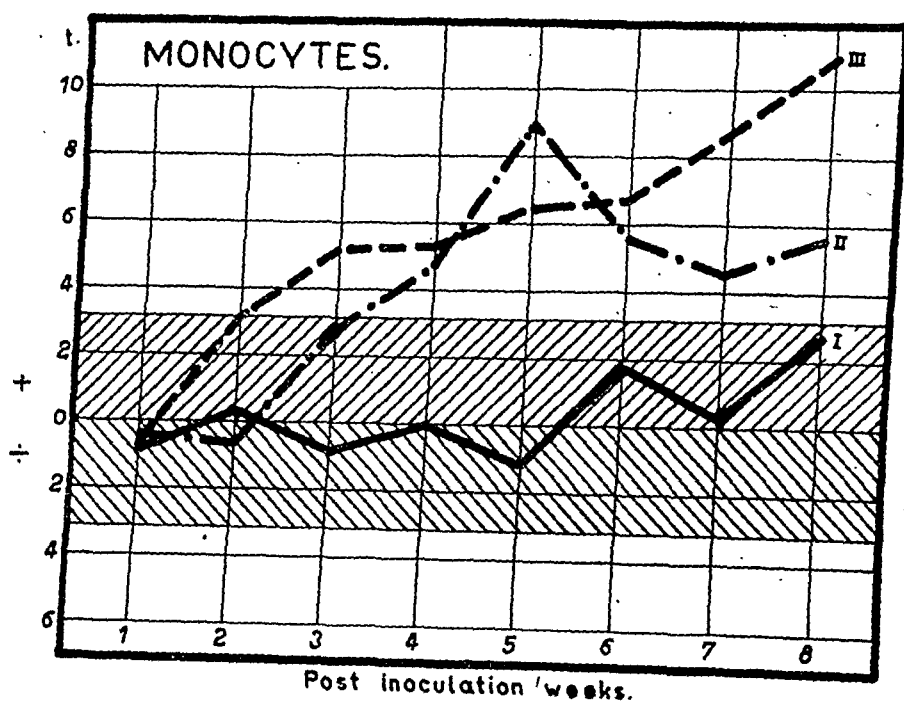


Chart 6.

The desensitized animals in group I showed at no time significant deviations from the base-line of the leukocytic index following the virulent inoculation. The allergic animals in group II showed consistently significant elevations from the base-line value

after the 24th day count. Thus the leukocytic index rose gradually from the base-line of 15.5 to 55.1 during the 58th post-inoculation count. The average leukocytic index value was 33.5 following inoculation and six of the eight mean post-inoculation values were significantly elevated, giving an efficiency of 75 percent. The low mean base-line leukocytic index in the control group III animals was due to the absence of abnormal leukocytic values before inoculation took place. Hence we find that after the intraperitoneal inoculation with virulent tubercle bacilli, all the mean values were significantly elevated, giving an average post-inoculation leukocytic index of 34.9 and 100 percent efficiency. Thus the Crawford-Medlar leukocytic index proved to be more sensitive than the monocytes in reflecting the course of pathological events in the three groups of animals (Table 1 and Chart 6).

*Monocyte-lymphocyte ratio (M/L):* In the desensitized group I animals we failed to observe any sustained rise in the M/L ratio after the virulent infection, but during the 45th and 58th post-inoculation days two peaks occurred, namely 0.234 and 0.245, only the latter of which was significant. Thus the post-inoculation average M/L value was only 0.172, which was only slightly higher than the base-line value of 0.161. Of the eight post-inoculation mean M/L values in the desensitized group only one was significant, giving an efficiency of 12.5 percent. In the allergic group II animals we observed an evenly sustained elevation of the M/L values, beginning during the 24th post-inoculation day with 0.291 and terminating on the 58th day with 1.082. Thus the average post-inoculation M/L value was 0.479 while the base-line value was 0.149. Six of the eight mean post-inoculation M/L values were significant, giving an efficiency of 75.0 percent. In the control group III animals, this spectacular elevation in the post-inoculation values was still higher and began already on the 17th day to become significant with 0.205 and thereafter continued unabated to rise to 2.642 on the 52nd day only to recede to 1.148 on the 58th day. The highest post-inoculation average M/L value was also recorded in this group, namely 0.747, while the base-line value was only 0.106. Thus seven of the eight post-inoculation M/L values were significant, giving an efficiency of 87.5 percent. This figure vies with that of the monocytes in the same group of animals for the second place as the most sensitive detectors of advancing tuberculous disease,



Table 3.

*Efficiencies in percent of blood cells and cellular ratios in showing abnormal values in experimental tuberculosis.*

|                                     | Iatergic-immune    |                   | Allergic-immune    |      | Allergic-control |       | Smithburn et al.   |
|-------------------------------------|--------------------|-------------------|--------------------|------|------------------|-------|--------------------|
|                                     | I                  | II                | I                  | II   | I                | II    |                    |
| Crawford's leukocytic index .....   | 18.19              | 0                 | 81.82              | 75.0 | 90.91            | 100.0 | —                  |
| Ratio monocytes-lymphocytes.....    | 18.19              | 12.5              | 72.43              | 75.0 | 90.91            | 87.5  | 89.47              |
| Monocytes .....                     | 36.37              | 0                 | 90.91              | 62.5 | 90.91            | 87.5  | 78.95              |
| Hemoglobin .....                    | 42.86              | 0                 | 71.43              | 50.0 | 71.43            | 75.0  | 63.15              |
| Erythrocytes .....                  | 14.29              | 50.0 <sup>1</sup> | 42.86              | 50.0 | 71.43            | 75.0  | 52.63              |
| Lymphocytes .....                   | 0                  | 0                 | 36.37              | 62.5 | 72.73            | 62.5  | 73.68              |
| Total white blood cells .....       | 72.73 <sup>3</sup> | 50.0 <sup>1</sup> | 90.90 <sup>3</sup> | 25.0 | 63.64            | 62.5  | 36.84 <sup>2</sup> |
| Neutrophiles .....                  | 0                  | 12.5              | 54.55              | 25.0 | 27.28            | 50.0  | 42.10 <sup>2</sup> |
| Ratio Neutrophiles-lymphocytes .... | 0                  | 12.5              | 9.10               | 25.0 | 63.64            | 50.0  | 57.89              |
| Eosinophiles .....                  | 0                  | 0                 | 0                  | 0    | 0                | 0     | 52.63              |
| Basophiles .....                    | 0                  | 0                 | 0                  | 0    | 0                | 0     | 42.10 <sup>3</sup> |

Series I refers to our previous article in *Acta Med. Scand.*, 1942, 110, 201, and series II to our present study.

Smithburn, Sabin and Hummel's series appeared in *Amer. Rev. Tuberc.*, 1937, 36, 673.

<sup>1</sup> Less reliable than might be indicated, since BCG-paraffin focus in left leg became abscessed, ruptured, and secondary infection occurred in fistule.

<sup>2</sup> Less reliable than might be indicated, since some values were high and others low, indicating that both determinations are subject to variation from a variety of causes, such as tuberculosis of the bone marrow, secondary infections, etc.

<sup>3</sup> Data open to question as base-line values were lower than those of Chasey and Pearce (*J. Exp. Med.*, 1930, 61, 97). Animals may have shown rise in basophiles due to influence of state of maturity.

<sup>4</sup> Significant deviations were in direction of an increase from base-line and thus differ from efficiencies in the allergic-immune and allergic-control groups which were in direction of a decrease.

but the first place goes to the leukocytic index, which scored an efficiency of 100 percent (Table 1 and Chart 7).

*Neutrophile-lymphocyte ratio (N/L):* Only one significant deviation from the base-line N/L value was registered in the desensitized group I animals, namely 11 days after the virulent infection, but in a descending direction. All the remaining seven post-inocula-

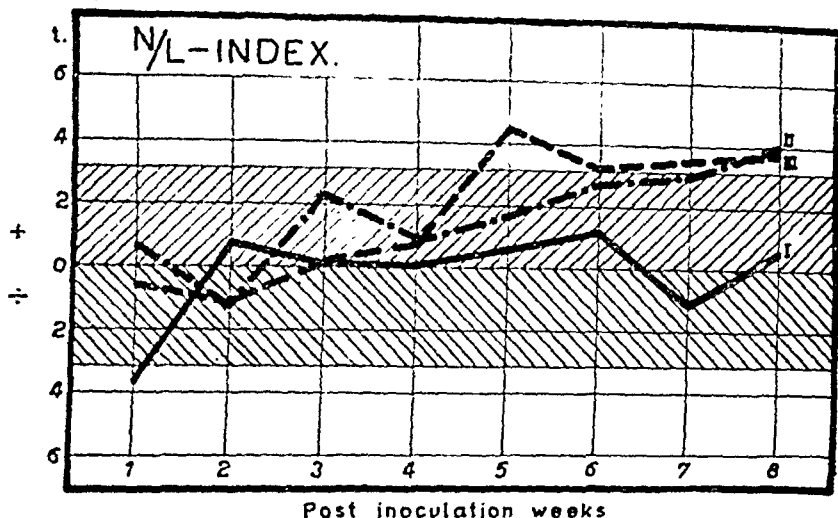
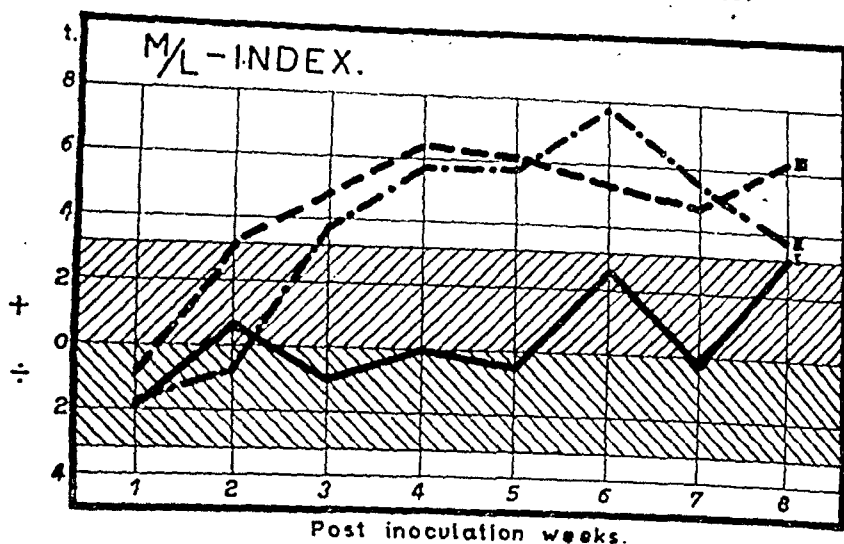


Chart 7.

tion N/L mean values were insignificant, making a total average of 1.538 while the base-line N/L mean value was 1.531. In the allergic group II animals we observed a steady rise in the mean N/L values beginning on the 24th post-inoculation day with 1.433 and terminating on the 58th day with 3.923. While the base-line N/L mean value was 0.963 in this group, the total post-inoculation mean value was nearly doubled, namely 1.885. But only two of the eight post-infection mean values were significant, giving an efficiency of only 25.0 percent. In the control group III animals, a more marked ter-

minimal elevation in the mean N/L values was noted and from a base-line mean N/L value of 1.046 the elevation reached 12.092 on the 52nd day. The total post-inoculation mean value was 3.054, or three times the normal base-line value. Four of the eight post-infection mean N/L values were significant, giving an efficiency of 50.0 percent.

Table 3 collates the efficiencies of blood cells and cellular ratios in desensitized iathergic-immune, allergic-immune and allergic-control guinea pigs in this present and the 1942 series, as well as the hematological efficiency data published by Smithburn, Sabin and Hummel (21) on tuberculous rabbits.

The significant changes in the blood picture, of leukopenia and extreme lymphocytosis, etc., which take place after the anaphylactic shock is induced in the anaphylactically sensitized iathergic-immune and allergic-immune guinea pigs, are so radically different from those recorded before the anaphylactic shock takes place, that a detailed description of these changes will be reserved for a subsequent publication.

### Discussion.

In order to correlate the blood picture occurring in the highly resistant tuberculous human being with that observed in the non-resistant tuberculous guinea pig, we have attempted to produce experimentally three grades of severity of tuberculous infection which approach the various types seen in man, namely, (1) the septic type of acute miliary tuberculosis or the very acute and rapidly advancing case of pulmonary tuberculosis, as represented by our allergic-control animal series; (2) the moderately resistant but progressive tuberculous disease undergoing abscess formation, as represented by our allergic-immune animal series; (3) the highly resistant non-septic and healing type of tuberculous infection as represented by the desensitized iathergic-immune animal series. By establishing the base-line of various blood cells and cellular ratios in these various animals which had been endowed with various degrees of resistance and susceptibility before the virulent test infection took place, we would be able to determine whether or not any significant and persistent deviations from the base-line values had taken place as a result of the tuberculous test-infection. Barring the disturbing

influence of intercurrent infection, we would thus be able to determine with certainty whether or not such deviations have any prognostic value. This procedure has been followed on several previous occasions in order to establish *intra vitam* proofs in support of our known pathological-bacteriological findings which made us conclude that the allergic state of hypersensitiveness is not, as many contend, essential for the full operation of resistance in tuberculosis.

In the present investigation we have observed a remarkable close correlation with the significant deviations in blood cells and cellular ratios elicited in the 1942 animal series. In the non-resistant allergic-control animals we found that the Crawford-Medlar leukocytic index (16 & 17), which these authors have tested on 281 cases of clinically active tuberculosis observed from 1 to 5 years after their discharge from the sanatorium, yielded the highest deviation efficiency, namely 100 percent, as a most reliable indicator of advancing tuberculous infection. In the moderately resistant allergic-immune animals the leukocytic index predominated with 75 percent deviation efficiency as the most reliable detector of the underlying pathological process. The remarkable feature, however, is that the leukocytic index showed no significant deviations from the normal base-line of the blood cells and cellular ratios in the highly resistant desensitized iatrogenic-immune animals. It should be recalled that the Crawford-Medlar leukocytic index is derived from the abnormal values of the neutrophile-lymphocyte ratio, the elevation of monocytes, and the abnormal total white cell counts. The significance of these four variables has been pointed out by Medlar (17) as follows: (1) »the neutrophile plays the chief rôle in tuberculous abscess formation and in the extension of tuberculous ulcers; (2) the lymphocyte predominates when the tuberculous lesion is healing; (3) the monocyte is the chief cell of new tubercle formation; (4) the total white cell counts roughly indicate the volume of deranged tissue with which the leukocytes have to cope». Thus, the leukocytic index represents theoretically a measure of the organism's resistance against tuberculous infection. In our studies we have been able to confirm Crawford and Medlar's contention of the excessive sensitiveness of the leukocytic index for advancing tuberculous infection.

The monocyte-lymphocyte ratio and the monocyte percentage follow as close seconds as reliable reflectors of advancing tuber-

culous infection. They are in fact more sensitive than the neutrophile-lymphocyte ratio, the hemoglobin, or any other blood cells alone. Thus, in the allergic-control animals the M/L ratio and the monocyte percentage scored the high figure of 87.5 percent efficient deviations from the normal base-lines. In the moderately resistant allergic-immune animals the M/L efficiency rate was 75 percent while the monocyte percentage scored 62.5 percent efficiency. But the remarkable observation was that the highly resistant desensitized iathergic-immune animals showed the low figure of 12.5 percent M/L efficiency and none whatsoever for the monocyte percentage. This fact merits the re-statement that the monocyte is the most sensitive of all the blood cells alone in registering advancing tuberculous infection and that the lymphocyte shows deviations which parallel the loss of resistance and hence the advance of tuberculous disease. These observations confirm the above mentioned classical investigations by Florence R. Sabin and her co-workers at the Johns Hopkins Medical School and at the Rockefeller Institute for Medical Research. Both in the non-resistant allergic-control and moderately resistant allergic-immune animals we observed 62.5 percent efficiency deviations in the lymphocytes in a downward direction during the test infection. During that same period no significant deviations in the lymphocytes were observed in the highly resistant desensitized iathergic-immune animals.

The microcytic type of iron deficiency anemia, which is characterized by a subnormal number of erythrocytes containing a subnormal amount of hemoglobin, presented 75 percent efficiency deviations in the non-resistant allergic-control animals and 50 percent in the moderately resistant allergic-immune animals. No significant deviations occurred during the test infection in the highly resistant iathergic-immune animals. We cannot account for the microcytic anemia because of the scarce tuberculous lesions in the bone marrow. Sabin, Doan and Cunningham (20) have suggested that this form of anemia is probably due to the toxic effects of the products of the tubercle bacillus.

The significant terminal increase in neutrophiles and its greater importance in the acute than in the chronic or retrogressive tuberculous lesions, as emphasized by Medlar and Sasano (22), Smithburn (23), and Smithburn, Sabin and Hummel (21), was confirmed by us in the present non-resistant allergic-control animals which scored

an efficiency of 50 percent. It was less pronounced in the moderately resistant allergic-immune animals (25 percent) and negligible (12.5 percent) in the highly resistant iathergic-immune animals. It is quite apparent that this retarded neutrophilia is associated with the fully established tuberculous disease while the changes in the monocyte occur very early in the infection when the first tubercles are being formed. The same relationship holds true for the progressive shift to the left of the immature band form of metamyelocytes.

Up to this point there exists a remarkable correlation between the Smithburn, Sabin and Hummel series (21) and our series of significant deviations of blood cells and cellular ratios during a test tuberculous infection. Our studies have been extended, however, to include the important Crawford-Medlar leukocytic index, and the Schilling formula for the shift to the left of immature neutrophils. We fail to confirm Smithburn and colleagues' observation of decline in eosinophiles during advanced tuberculous infection. This discrepancy may partly be due to their employment of the rabbit, and partly to their mode of calculating the total number of eosinophiles on the basis of the actually observed percentages of this cell, a fact to which we have already alluded in this article.

Besides having re-confirmed the immense value of a carefully conducted study of the blood cells and cellular ratios as an aid in prognosis in tuberculosis, we have also found such a study of diagnostic importance in differentiating between the highly resistant state of iathergic-immunity which is free from allergic hypersensitiveness, the moderately resistant allergic-immune state, and the none-resistant allergic-control state. By these means we have re-confirmed our conclusions based upon pathological-bacteriological data that immunity in tuberculosis may persist intact after the abolition of allergic and anaphylactic hypersensitiveness. Hence we maintain that immunity, allergy and anaphylaxis in tuberculosis are dissociable conditions most likely produced by specific antigens.

### Summary.

A hematological study made on highly resistant iathergic-immune (desensitized), moderately resistant allergic-immune, and nonresistant allergic-control guinea pigs, inoculated with human tubercle bacilli, revealed the following significant deviations in blood cells and cellular ratios from the normal base-lines:

1. The Crawford-Medlar leukocytic index, registering abnormal deviations of neutrophiles, lymphocytes, monocytes and total white cells, records most accurately the trend of advancing tuberculous infection.

2. The monocyte-lymphocyte ratio and the monocyte percentage attain to the second highest position as reliable indicators of advancing tuberculous disease.

3. The microcytic type of iron deficiency anemia, characterized by a subnormal number of erythrocytes containing a subnormal amount of hemoglobin, is equally shared by the erythrocytes and hemoglobin during tuberculous infection, but is less sensitive than the monocyte-lymphocyte ratio and the monocyte percentage.

4. The significant increase in circulating monocytes appears a considerable time before the decline in lymphocytes occurs. The latter is a better prognostic aid inasmuch as advancing lymphopenia is commensurate with loss of resistance.

5. An increase in neutrophilia and immature band forms of metamyelocytes occurs when the tuberculous disease is fully established.

6. Significant changes in blood cells and cellular ratios appear slower in the moderately resistant allergic-immune animals than in the non-resistant allergic-control animals, but both reveal essentially the same patterns of blood changes.

7. The highly resistant iathergic-immune (desensitized) animals show relatively few significant deviations in blood cells and cellular ratios during the test infection when the allergic-immune and allergic-control animals present excessive blood changes.

8. The hematological study supports the pathological-bacteriological data that immunity in tuberculosis operates at best advantage when the allergic state of hypersensitiveness has been abolished.

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From the Eye Department of the City of Oslo Hospital, Ullevål.

# Clinical Investigations of Methyl Alcohol Poisoning with Special Reference to the Pathogenesis and Treatment of Amblyopia.

By

OLUF RØE.

(Submitted for publication January 18, 1943).

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## I. Introduction.

During the five last decades, several investigators have studied methyl alcohol poisoning both clinically and experimentally. Yet there seem still to be widely divergent opinions as to the causes of the toxicity of methyl alcohol.

Apparently the reaction to the drinking of methyl alcohol varies greatly in different individuals. Uhthoff (50) found in a mass outbreak that only about one quarter of the drinkers fell ill, and yet their consumption of alcohol did not differ appreciably from that of the rest. Goldflam (13) noted that even if the severity of the poisoning was usually proportional to the amount of methyl alcohol consumed, some patients were dangerously ill even after small doses. Poulsson (38) states that alarming symptoms have been observed after 11.5 g, and according to Ziegler (57) one teaspoonful of pure methyl alcohol can provoke blindness.

These and several similar observations have led to the general assumption that individual predisposition to this poison varies greatly. In his discussion of the serious prognosis, Jackson (21) writes: »Idiosyncrasy plays a large part in the condition, and what might be an innocuous dose for one person might be fatal for another.»

This view does not, however, tally with Pohl's (37) statement: »Die biologische Bewertung der Alkohole hängt ganz ab von der Dosis in der sie aufgenommen werden.»

If this ruling is applicable to methyl alcohol, the general belief that its toxicity varies in different persons must be incorrect. In which case the most varied course of the poisoning must depend on other factors than the methyl alcohol itself.

Brückner (6) has, in opposition to other writers, evidently not been convinced as to the soundness of the theory that individual predisposition is of importance to the course of the poisoning, for he writes: »Disposition und Idiosynkrasie sind Umschreibungen die gegenüber so unterschiedlicher Wirkungsweise nichts erklären können.»

There are great differences of opinion as to the causes of the toxicity of methyl alcohol. While Pohl (35), Krohl (27) and Schmiedeberg (cit. Krohl) consider that its toxicity depends on formic acid, Brückner (6), Flury and Wirth (10) and Kazas (24) maintain that formaldehyde is the potent agent. Egg (9) considers that it is the methyl alcohol which is toxic. He assumes that it forms a complex compound with the iron in the granules of the cells resulting in inhibition of the processes of oxidation. He finds that formic acid is present in too small quantities to be injurious.

The divergent opinions of different writers as to the mode of

action of methyl alcohol betray many gaps in our knowledge of the processes of poisoning with this substance.

We do not yet know why methyl alcohol exerts a selective action on the retina.

## II. The Object of the Investigations.

The long latent period is one of the characteristic features of this form of poisoning. This period usually lasts some 24 hours, and is not infrequently a matter of several days. During this period it is possible that other factors than the methyl alcohol itself influence the course of the poisoning.

It is primarily a solution to this problem which has been sought in the present study.

Many of the patients were chronic tipplers. Some of them would, as a rule, drink ordinary alcohol even before feeling unwell after the poisoning. Hence the need of an investigation of the action of ethyl alcohol on methyl alcohol poisoning.

Others among the patients did not usually drink much alcohol. They would, as a rule, go to their work on the day after the poisoning, whereas the chronic tipplers would, for the most part, always be out of work. Hence the call to investigate the influence, if any, of muscular action on the course of the poisoning.

It is blindness, and only this, which renders those who survive this poisoning invalids for life. This is why special interest attaches to the pathogenesis of this condition.

Is there, in the first place, any relationship between the severity of the general symptoms and the degree of the amblyopia? In the second place, are there other factors of importance in the development of amblyopia? This may well be so, for there are cases on record in which amblyopia occurred in the absence of other serious signs of poisoning. In this connexion the part light may play in the genesis of amblyopia will be discussed.

In the follow-up investigations, it has seemed advisable to elucidate the course of the amblyopia. This line of research does not hitherto seem to have been followed over a long period after the poisoning. Even though failing sight has often been observed in these cases after the first period of improvement, it is assumed that there are some patients who retain the vision they regain

(Rönne and others). Further knowledge on this score would greatly facilitate the prognosis.

Finally an attempt will be made to give a theoretical explanation of the selective action methyl alcohol exerts on the retina and the optic nerve.

### III. The Methods Employed.

Great importance has been attached to obtaining as complete records as possible of cases. Hospital records, being often scanty, have been supplemented by information obtained from the patient after the acute stage of the poisoning. Many of these patients, however, suffer from marked amnesia, and the value of their evidence may therefore be called in doubt. The patients' relations and boon companions have, accordingly, been written to or interviewed whenever possible.

Special importance attaches to the information given by those boon companions who did not themselves fall ill. They have, as a rule, been able to state how much the patient drank, and how much they themselves drank of spirits containing methyl alcohol and ordinary alcohol. This information has been useful in seeking an explanation for the diversified manifestations of the poisoning.

Exact data have also been needed for timing the onset of visual disturbances in relation to the general symptoms — an important point in determining the part played by acidosis in the development of amblyopia. Without these data it would be impossible to form an opinion on this point in those cases in which the general manifestations had wholly or partly disappeared on the patient's admission to hospital.

The findings of the clinical examinations and blood tests have been obtained from hospital records. In a couple of cases, and at the author's request, the lactic acid content of the blood was determined.

The ophthalmological examinations have been carried out by myself on all the patients who survived the poisoning. Data concerning patients Nr. 1 and 2, who had been treated in other hospitals before admission to Ullevål, have been obtained from that source. Abstracts have been made from the records of two cases already published, by Harboe (16) in 1920, and Ustvedt and Mohn (52) in 1932.

After correction of refraction errors, vision was determined by Snellen's types, finger-counting, movements of the hand and light. By «normal vision» is meant 6/6 even though this is not, scientifically speaking, strictly identical with full acuity of vision.

The field of vision was examined according to Donders' method in the hospital wards. When, at a later date, it was examined at the Eye Department, the perimeter and Bjerrum's screen were used.

During their treatment at Ullevål, the eyes of nearly all the patients were protected against light, those who suffered from amblyopia wearing darkened spectacles also after discharge from hospital. For the examination of the acuity and field of vision, the patients were given about 10 minutes in which to adapt themselves to the illumination employed.

The perimeter was placed between two electric bulbs, each of 100 watt, to make its illumination as constant as possible. The distance from each of these bulbs to the perimeter was about one meter. The bulbs were raised or lowered a little when necessary to avoid a shadow being cast by one half of the perimeter arc on the other.

It soon became evident after the first examinations that the acuity of vision of the periphery of the retina was surprisingly high even when central vision was much reduced. Use was therefore made of a 10-millimeter object when the outer limits of the field of vision were investigated.

It was also found that, on testing with Bjerrum's screen, it was convenient to use the same object, as the limits for the scotomata, notably the relative scotomata, could be determined with greater precision than with larger objects.

When a scotoma is central and absolute, one cannot be sure that the fixation mark on Bjerrum's screen lies in the prolongation of the optic axis of the eye. It is therefore doubtful if the scotomata found are in reality in that part of the field of vision indicated on the charts. This possible source of error is to a certain degree corrected, after a preliminary determination of the approximate size of a scotoma, by drawing a white cross whose crucial point coincides with the fixation mark. This cross is drawn a little larger than the scotoma in question. The patient is then told to adjust his vision in such a way that he can just see the four ends of the cross.

When the amblyopia has lasted a considerable time, the acuity of vision is registered graphically from the date of admission to hospital in periods of two to three months. On these graphs, the starting point coincides with the day of the poisoning, the absciss with the time, and the ordinate with the acuity of vision.

#### IV. Case Records.

The material studied consists of 16 patients suffering from methyl alcohol poisoning. Cases Nr. 15 and 16 have already been published and are the only cases of methyl alcohol amblyopia hitherto on record in Norway.

The other 14 patients were treated at Ullevål Hospital between July 31, 1941 and April 14, 1942. Two of these patients (Nrs. 1 and 2) had been treated at other hospitals during the acute stage of the poisoning, whereas the other 12 were admitted direct to the medical wards of Ullevål Hospital.

In the discussion of the pathogenesis of the poisoning, brief reference will be made to two patients who were treated on the medical side of Drammen Hospital in November 1941.

##### Case 1.

Reference number 11883/41 — S. K. A man, unemployed, aged 56.

On May 4, 1941, he drank about 90 cm<sup>3</sup> of methylalcohol destined as a freezing solution for motor cars. He knew it was wood spirits he was drinking, and he said that he did not become intoxicated.

On the morning of May 5, he felt well and went down to the sea shore to attend to a boat. The sun was shining. After spending a couple of hours on the piers, he suddenly noticed that his vision became cloudy. After he had returned home at midday, he was seized by an attack of vomiting, severe thirst and breathlessness. He had the same symptoms on May 6 when, according to his wife, he was very drowsy. This he could not remember himself. On May 7, vision was much reduced, whereas the other symptoms showed improvement. It was not till May 8 that he was admitted to the Eye Department of the Rikshospital. He was now blind. He gave no information concerning his consumption of methyl alcohol.

On May 8, an ophthalmological examination showed normal externa and clear media. The pupils were dilated, reactionless. The optic discs were injected, their limits blurred, with slight oedema around them. The size of the arteries was normal, but there were some small, punctiform haemorrhages scattered along the blood vessels. The veins were well filled. Vision = 0. o. u. (both eyes).

Blood pressure 135/90 Hg. Normal findings on clinical examination. A trace of albumin in the urine.

On May 16, a neurological examination showed left-sided hyposmia, right-sided deviation of the tongue and palatine raphe, as well as increased patellar and Achilles reflexes on the right side.

A radiological examination of the cranium showed nothing amiss, and the cerebro-spinal fluid was normal. Wassermann negative in blood and cerebro-spinal fluid. He was discharged on June 14. Vision o. s. (left eye): Finger-counting at 1 meter. o. d. (right eye): Finger-counting  $\frac{1}{2}$ m.

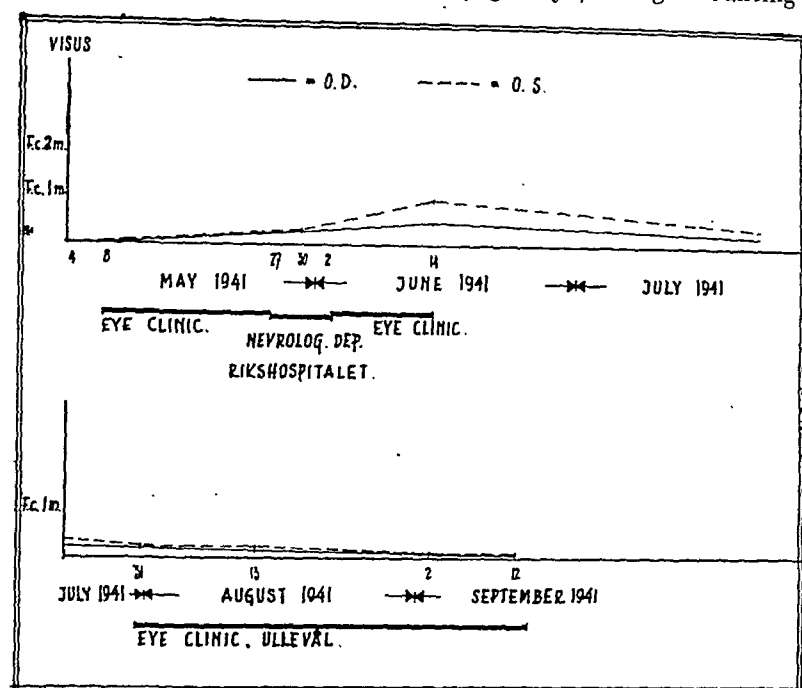


Fig. 1. Case 1 — S. K. F. c. = Finger-counting.

On his admission to the Eye Department of Ullevål on July 31, the pupils measured 5.5 mm, reacting feebly to light. The optic discs were sharply defined, fairly pale, the blood vessels thin and uneven in calibre. As the chart shows, vision declined after his stay in the Rikshospital, and it continued to do so during his stay at Ullevål Hospital.

He was treated with potassium iodide and sweat baths, and he was also given injections of vitamin B<sub>1</sub>.

Analysis of the spirits revealed pure methyl alcohol. He was discharged on September 13, 1941.

The alkali reserve was not investigated in this case, but the symptoms indicated severe acidosis before his admission to hospital.

Some time later he was admitted to the Psychiatric Department for depression and insomnia. On re-examination on February 21, 1942, there was weak perception of light on both sides and projection of light upwards.



**Case 2.**

Reference number 16100/41. K. L. L. A workman pensioner, aged 61.

The patient, a chronic drunkard, was transferred from the Eye Hospital at Hamar. On August 25, he travelled from Oslo to Hamar on a visit to his daughter. Next day he slept much more than usual, and had to be awoken whenever he was served with food. On August 27, there was no change in his condition. On his admission to hospital on August 28, he denied having drunk methyl alcohol, but he admitted that, two days before his journey to Hamar, he had drunk a couple of bottles of beer and some «akevit» — potato spirits.

There was bilateral amaurosis, with injection of the optic discs whose limits were somewhat ill-defined. The fundus was in other respects normal. A slight degree of vision returned gradually, and on September 29,

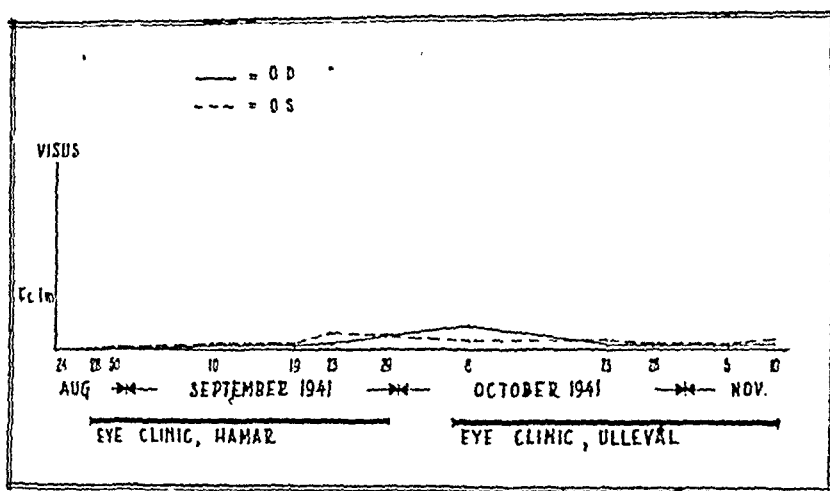


Fig. 2 Case 2, K. L. L. F. c. = Finger-counting.

he could count fingers at 30 cm with either eye. On the same date some limitation of the outer limits of the field of vision and an absolute central scotoma were demonstrable.

On coming to the Eye Department of Ullevål on October 7, the patient looked well. Pulse 48, regular. Temperature 36.5° C. Blood pressure 145/75 mm Hg.

The clinical findings, including the urine analysis, were normal. Apart from the eyes, the neurological examination proved negative. A skiagram of the cella turcica and sinuses was normal. In the blood and cerebrospinal fluid Wassermann was negative.

The ophthalmological examination showed normal externa, pupils about 4 mm, with sluggish reaction to light. The optic discs were pale and excavated, with atrophic blood vessels.

The chart shows the course of vision.

He was treated with preparations of vitamin B<sub>1</sub> and roborants.

This patient also showed signs of a severe poisoning. He was late in coming for treatment and is practically blind.

**Case 3.**

Reference number 16952/41 — G. H. A man, bookbinder, aged 32.

He had hitherto been well, and vision had been good. On the evening of October 18, 1941, he shared with three companions spirits brought in two beer bottles. He believed he drank two tumblersful of a mixture of spirits and lemonade, in the proportion of 1 to 2.

He did not become intoxicated, but he felt tired and went to bed at 23 o'clock. He slept till 14 o'clock next day when he suffered from headache and nausea, and saw black spots before his eyes. Having eaten a little, he fell asleep again. On October 20 he felt tired, could not go to work, and had misty vision.

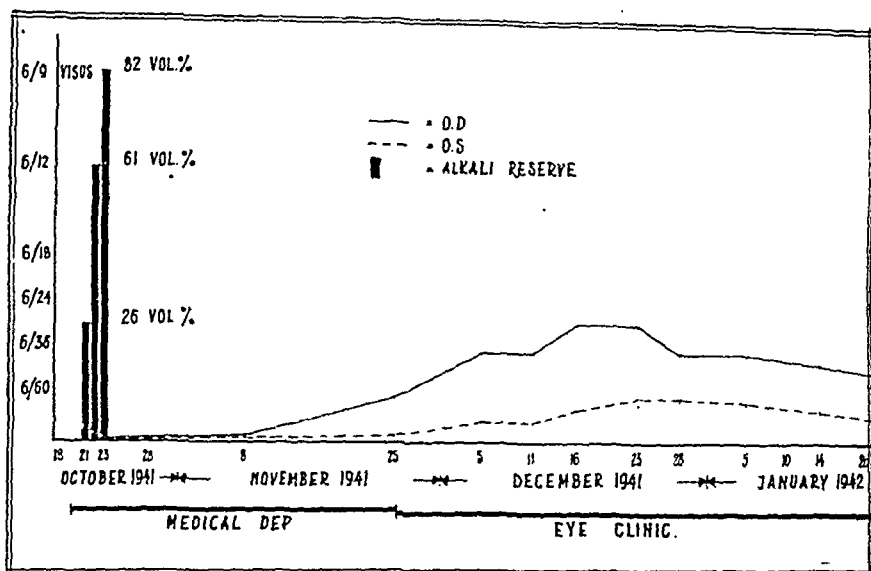


Fig. 3 Case 3. G. H.

On admission to hospital on the same day, he could give a clear account of himself though he felt tired and drowsy. Though vision was poor, he could read a newspaper. He complained of pressure over his eyes. Pulse 90 and regular. Temperature 37.7° C. Respiration not embarrassed (respiration rate not recorded). Blood pressure 150/100. Pupils equal and dilated, reacting to light and accommodation. The clinical findings, including the urine analysis, were normal.

Ophthalmological examination was not performed till October 21 at 14 o'clock. He was then very restless, throwing himself about in his bed. There was severe dyspnoea with markedly deep respiration.

The ophthalmological examination showed normal externa and clear media. The pupils were equal, 6 mm, reacting very sluggishly to light. The outlines of the injected optic discs were ill-defined. There was considerable oedema about the optic discs and in the central portion of the fundus. The appearance of the arteries was normal, the veins were slightly dilated.

Vision: Finger-counting 1.5 m for both eyes. The limits of the field of vision and the tension were normal.

The alkali reserve was not investigated till the morning of the day after admission when it was 26 volumes per cent. In the course of this morning his condition became rapidly worse and he was, as already stated,

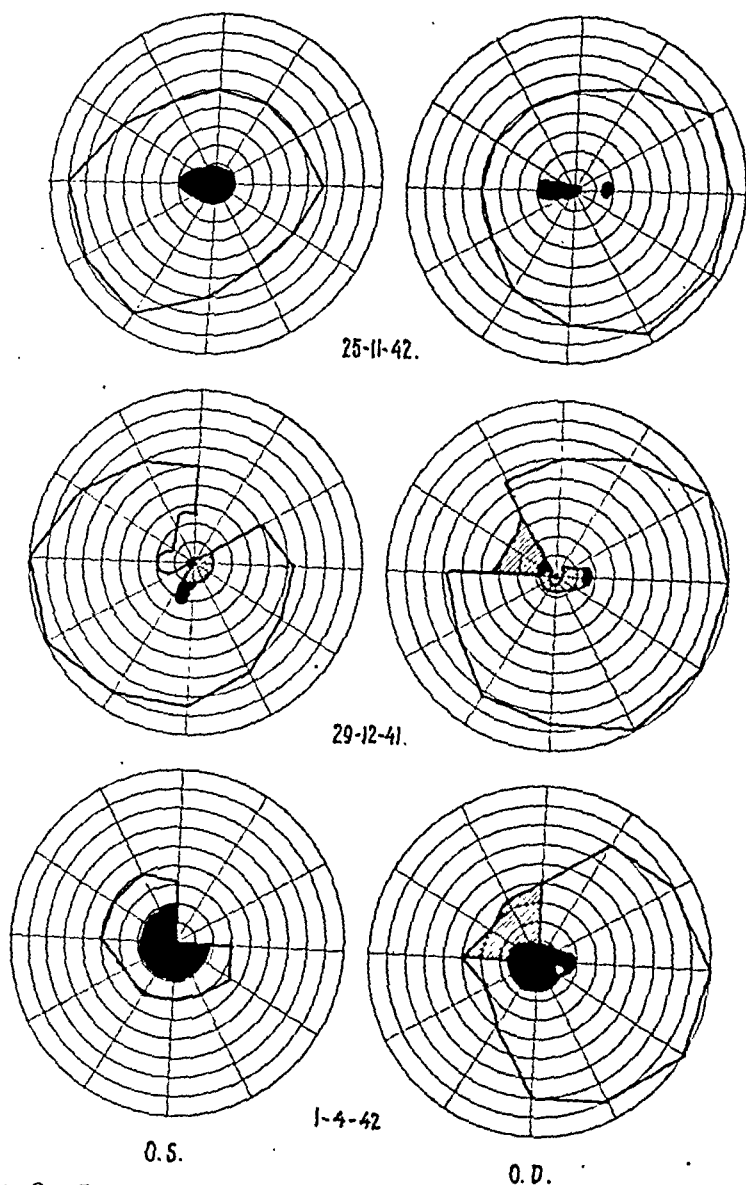


Fig. 4. Case 3. G. H. — Size of objects 10/330 and 20/1150. Red-green blind. Central scotoma for blue.

very exhausted and dyspnoeic at 14 o'clock. It is therefore probable that the alkali reserve was lower at this stage, but apparently further examinations were not carried out on this day.

On October 21, he was given  $\text{NaHCO}_3$  10 g  $\times$  4 by the mouth and 1000  $\text{cm}^3$  of a 5 per cent. glucose solution by intravenous injection. On the two following days he was given  $\text{NaHCO}_3$  5 g  $\times$  3 by the mouth.

On November 25 he was transferred to the Eye Department. An ophthalmological examination showed normal blood vessels and no marked pallor of the optic discs. The course of his vision during his stay in hospital is indicated on the chart.

December 28: The optic discs are sharply defined, with considerable pallor, notably in the temporal region. The arteries are abnormally thin and their calibre is irregular. Both the inferior temporal arteries resemble wire-thread arteries. The left is obliterated, the right transmits little blood. The veins are well filled and show calibre variations, the course of the small veins being tortuous. The state of the visual field is seen in the following chart.

On re-examination on September 15, 1942, O. s.: Perception of light, o. d.: Finger-counting 1.5 m.

The patient stated that the three companions with whom he had caroused had between them drunk a bottle of »akevit» (potato spirits = 750 cm<sup>3</sup> 42 vol. per cent. ethyl alcohol) just before they had joined him. Each of them had therefore consumed about 100 cm<sup>3</sup> of ethyl alcohol. The patient thought that these three had drunk about the same quantity of methyl alcohol, whereas he himself had drunk less. Two of his companions did not fall ill, but they told him later that they had both felt enervated on the day after the spree, and one of them had suffered from nausea and severe headache. Shortly afterwards, both these men went to work elsewhere, and it was not till September 1942 that they were traced. They confirmed the patient's statements, adding that on the day after the poisoning each of them had drunk two glasses of heady wine, one dram of »akevit» and half a litre of Pilsner beer at a restaurant. On the following day they had drunk two glasses of heady wine and half a litre of Pilsner beer. Neither of them had suffered from disturbances of vision.

The third companion, who had brought the spirits, was admitted to hospital on the same day as the patient, dying shortly after admission. After his death a beer bottle, which still contained some spirits, was found in his home. Analysis revealed 62 weight per cent. of methyl alcohol.

#### Case 4.

Reference number 20371/41 — B. D. Woman, aged 40.

The patient was admitted to hospital on December 9, 1941, in the company of her cousin who stated that she had been much out on the spree of late. She had not been at home for some days, and had returned one morning obviously exhausted. She lay down to sleep, and did not awake till the afternoon. She complained of feeling very ill, of abdominal pain and of laboured respiration.

On admission to hospital at 20.45 o'clock, she did not react to speech or pin-pricks. Her dilated pupils were reactionless. Her respiration was superficial and intermittent, and her lips and limbs were cyanosed. The alkali reserve in the blood in a double test was 9 volumes per cent. Formic acid in the blood 19 mg per cent.

She was at once given 5 cm<sup>3</sup> of coramin by intravenous, and lobelin by subcutaneous injection. The pulse steadily became weaker, the cyanosis increased, and the respiration became more intermittent. Death occurred at 21.05 o'clock after a couple of attacks of general clonic convulsions of small degree.

Methyl alcohol was found in the stomach and urine. The necropsy showed cyanosis of the organs and purulent salpingitis.

### Case 5.

Reference number 20322/41 — K. B. A workman pensioner, aged 69.

Hitherto well. He admits habitual drinking, and frequent indulgence in denatured spirits.

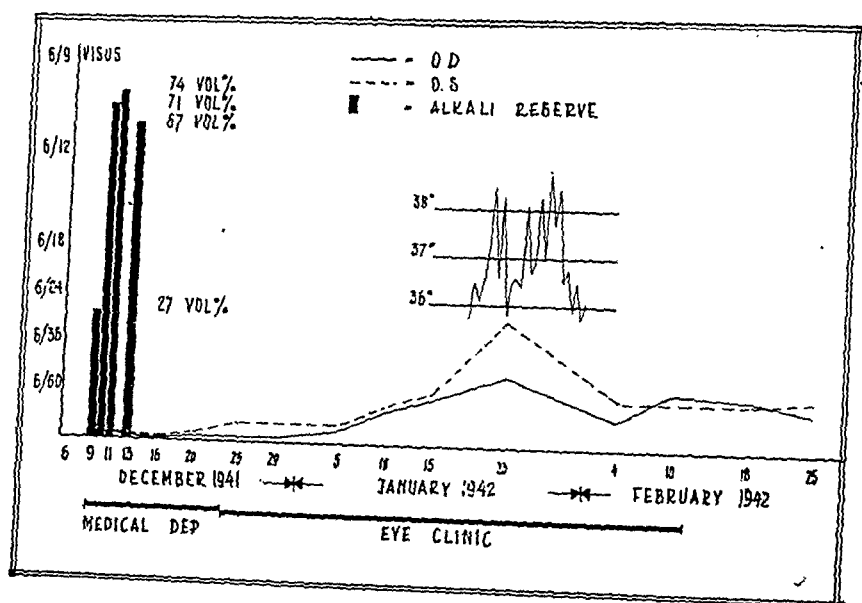


Fig. 5 — Case 5 — K. B. The development of a febrile sore throat coincided with a strikingly rapid diminution of vision.

On December 6, 1941, in the company of three strangers, he drank spirits mixed with coffee, the combination tasting of perfume. He did not become intoxicated. Next day he again drank the same mixture. On the night between December 7 and 8 he was awoken by nausea and vomiting, and he noticed that his vision was impaired. He slept almost the whole day of December 8.

On his admission to hospital on December 9, he had only slight perception of light. Accompanied by a friend, he walked into hospital, a man in fairly good condition, of a ruddy complexion. Pulse 80 and regular. Temperature 37° C. No embarrassment of the respiration whose frequency was not recorded. Blood pressure 130/80. The dilated pupils were reactionless. The clinical findings, including the urine analysis, were normal. The ophthalmological examination on December 10 showed normal externa and clear media. The right pupil 5 mm and reactionless;

the left 6 mm reacted feebly to light. The limits of the hyperaemic optic discs were blurred. The appearance of the blood vessels was normal. Vision O. s.: Finger-counting 30 cm. O. d.: Feeble perception of light. The field of vision O. s.: Normal (Donders) O. d.: Uncertain light projection. The tension felt somewhat reduced on both sides.

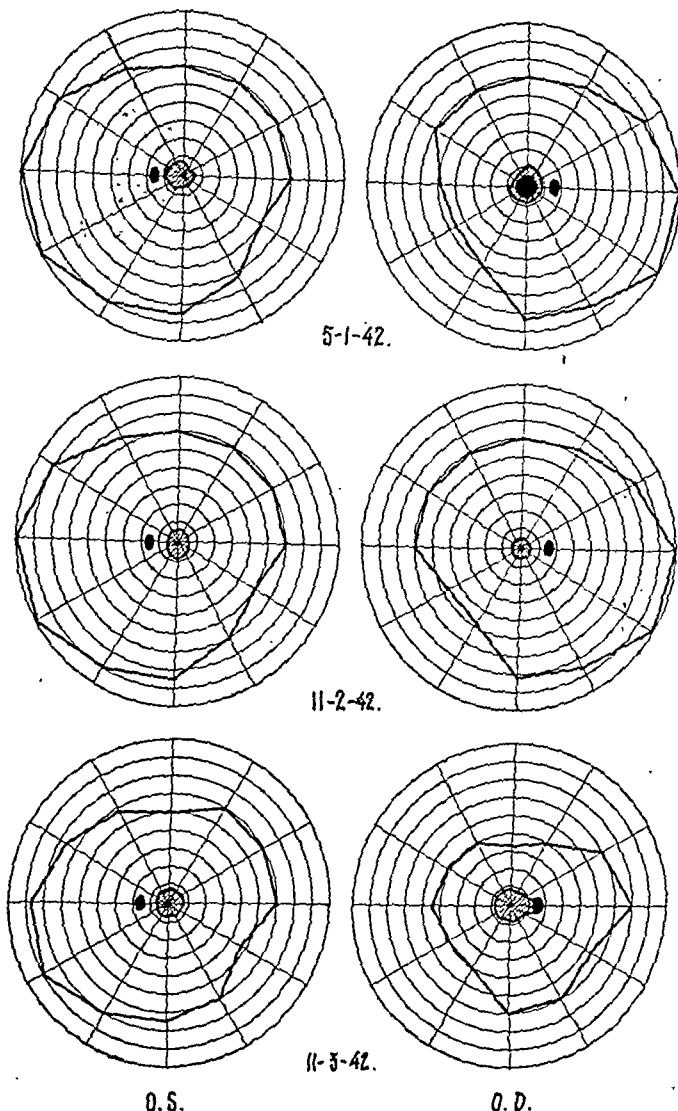


Fig. 6 — Size of objects 10/330 and 10/1150. Red-green blind. Febr. 11. Central scotoma for blue with almost normal outer limits.

He was treated with  $\text{NaHCO}_3$  10 g  $\times$  2 given by the mouth on the first two days, 10 g  $\times$  1 on the third day.

On December 24, he was transferred to the Eye Department. On January 5, the optic discs were possibly a little paler than normal, but there were no visible changes in the blood vessels. On February 10,

the optic discs were white and the blood vessels atrophic. The chart shows that the vision decreases after January 23.

The field of vision: See fig. 6.

He received 12 injections of vitamin B<sub>1</sub>, each of 20 mg while in hospital.

Vision gradually diminished after his discharge. At the last examination on September 25, 1942, vision O. s.; F. c. 1 m O. d.; F. c. 1.5 m.

#### Case 6.

Reference number 20389/41 — H. D. A man, proprietor of a workshop, aged 59.

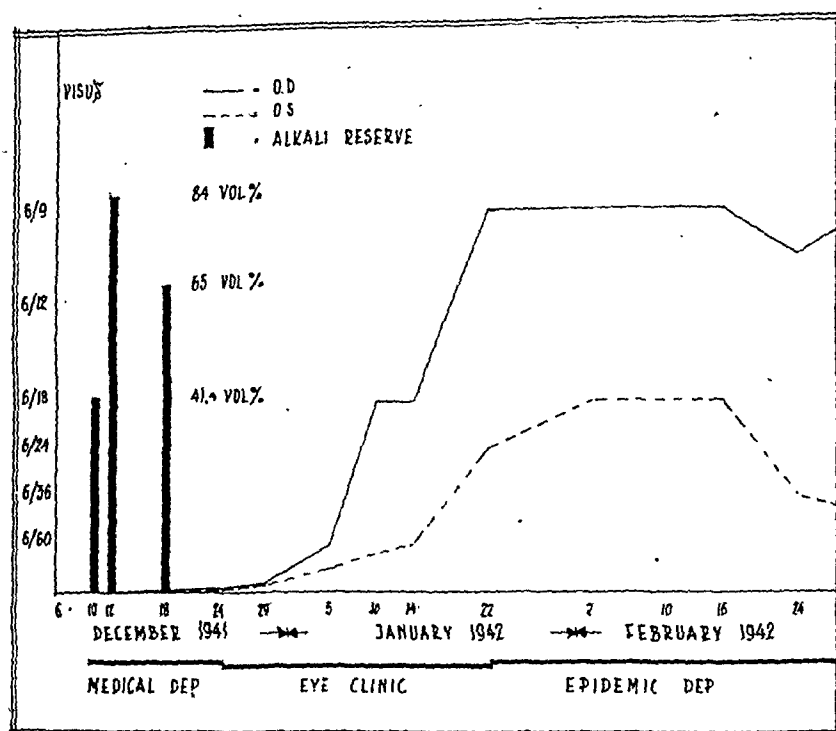


Fig. 7 — Case 6 — H. D.

He had hitherto enjoyed good health and vision. On December 6, 1941, a stranger entered his workshop and offered him spirits of which he drank about a tumblerful without becoming intoxicated. The spirits tasted of gin.

He was unwilling to part with his visitor who felt ill towards evening, and they both turned in to sleep at the workshop. He did not awake next day till 10 o'clock, and the visitor was then dead. Though he felt well, he was very depressed by this death, and he did no work on the following days, spending some time in bed and eating as usual.

On the afternoon of December 8, a man turned up and asked him to carry out an autogen welding. He went with him to the workshop, and as he was about to weld, his sight failed him so much that he could not continue his work. He wore the protective glasses which he generally employed.

On December 9, there was still further loss of vision, and he suffered from nausea, breathlessness and trembling of the legs. He applied to an emergency medical post where he was advised to seek admission to hospital. As he left this post, he felt as if he was falling. He drove to his home

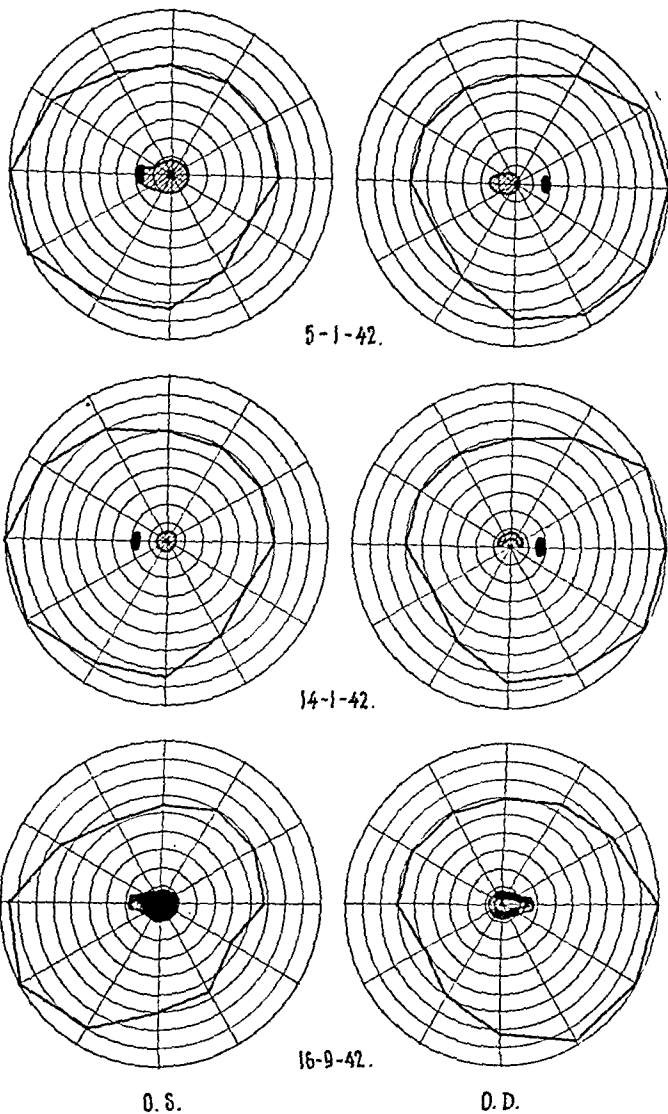


Fig. 8. — Case 6 — H. D. Size of objects 10/330 and 10/1150. Red-green blind.

and went to bed. Next day the general symptoms had vanished, but he was now blind. On coming to the Eye Department, he was at once recommended treatment in the Medical Department.

On December 10, he was admitted to hospital. He seemed to be fit and without general symptoms. The pulse was 100 and regular. The temperature was  $37.8^{\circ}\text{C}$ , and the blood pressure 160/110. The respiration



was not embarrassed, its rate not recorded. The clinical findings, including the urine analysis, were normal.

The ophthalmological examination showed normal externa and clear media. The round and dilated pupils were reactionless, and the limits of the injected optic discs were ill-defined. The appearance of the blood vessels was normal. Vision of both eyes: 0.

He was given an intravenous injection of 1000 cm<sup>3</sup> of a 5 per cent. solution of glucose, and NaHCO<sub>3</sub> 5 g  $\times$  3 by the mouth from December 10 to 18.

He was transferred on December 24 to the Eye Department. For acuity of vision see chart. (Fig. 7).

On January 22, he was transferred to the Epidemic Department as diphtheria bacilli had been found in the fauces.

As the chart shows, the vision of the left eye improved gradually till February 16. From that date the vision of the right eye also diminished slightly, but it was again 6/9 on March 5. Since then vision has diminished, and at the last examination on September 16, 1942, O. s.: Finger-counting 1 m. O. d.: 6/18  $\div$ .

It was noted on March 5 that the colour of the right optic disc was quite good and the appearance of the blood vessels normal. The left optic disc was pale, and the thick-walled arteries showed calibre changes, notably near the optic disc.

The field of vision: See fig. 8.

He was treated at the Eye Department with injections of vitamin B<sub>1</sub> and a few sweat baths.

In this case it was remarkable that the patient noticed his failure of vision at the moment when he looked at the welding light, and that the other symptoms did not appear till more than 12 hours later.

#### Case 7.

Reference number 20/519/41 — A. K. A salesman, aged 44.

He suffered from syphilis in 1922, and had been subject of recent years to «chronic bronchitis.» He was a chronic alcoholic and had often drunk denatured spirits. On December 9, 1941, he wanted to buy a bottle (750 cm<sup>3</sup>) of denatured spirits at a colour-shop. But by a mistake of the shop he was sold methyl alcohol. On the same day he drank about 100 cm<sup>3</sup> of it mixed with coffee. On the morning of December 10, he felt unwell and his vision was cloudy. On this day also he drank a considerable quantity of the spirits, and he admitted to the police that he had drunk a total of 250 cm<sup>3</sup>. He confessed later to having consumed at least 300 cm<sup>3</sup>.

Becoming steadily worse in the course of the day, he wondered if ordinary alcohol would not restore him to health. He drank five glasses of port wine at a neighbouring restaurant (about 300 cm<sup>3</sup> 18 vol. per cent. of ethyl alcohol). During the night he was but partially conscious, walking about at times. He did not remember this. On the morning of December 11, he was still very ill and drank a tumblerful of gin (about 150 cm<sup>3</sup> 45

vol. per cent. ethyl alcohol). A friend having called on him with some 96 per cent. spirits, he partook also of this beverage, he knew not how much. On the morning of the same day he was admitted to hospital.

On admission he was only partially conscious, and his face was very flushed. The pulse was 96, regular. The temperature was  $36.4^{\circ}\text{C}$ , and the blood pressure 125/100. The respiration was 32 and laboured. Apart from numerous adventitious sounds heard over the lungs, the clinical examination was negative.

A radiological examination showed bilateral infiltration of the apices and a cavity in the left lung. Tubercle bacilli were found in the sputum.

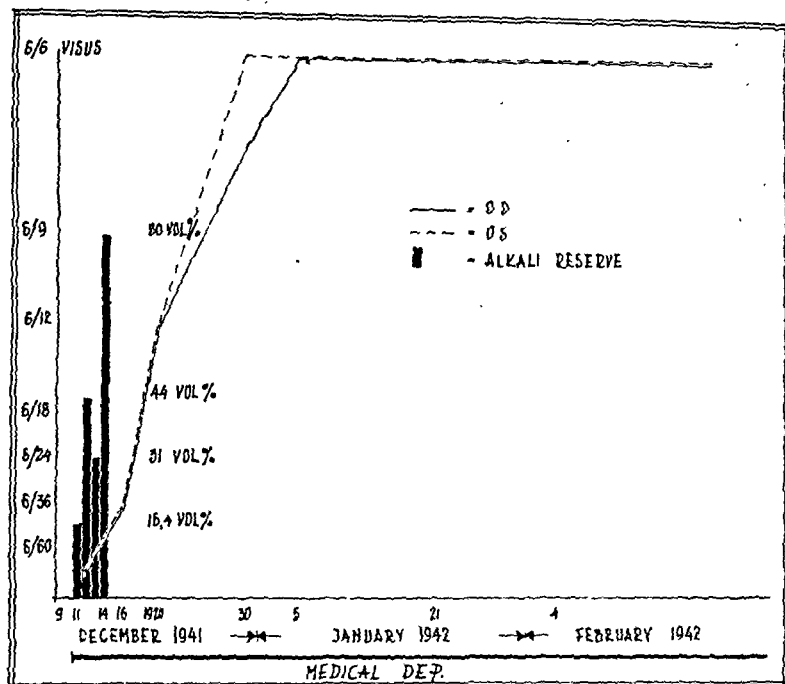


Fig. 9 — Case 7 — A. K.

On December 12, an ophthalmological examination showed normal externa apart from a marked vertical and rotatory nystagmus. The media were clear. The pupils were dilated, 7 mm, reacting feebly to light. The outlines of the injected optic discs were blurred. Finger-counting 3 m. O. u. The limits of the field of vision were normal (Donders). Tension on palpation satisfactory. The nystagmus disappeared after about a fortnight.

As the chart shows, there was a rapid improvement of the vision.

On December 11,  $\text{NaHCO}_3$  10 g  $\times$  4 was given by the mouth and 1000  $\text{cm}^3$  of a 5 per cent. solution of glucose by intravenous injection. On December 12,  $\text{NaHCO}_3$  5 g  $\times$  3. On December 13,  $\text{NaHCO}_3$  10 g  $\times$  4. On December 14,  $\text{NaHCO}_3$  10 g  $\times$  2.

On December 12, the methyl alcohol content of the blood was 0.14 per cent.

On re-examination on June 8, 1942, his vision was normal.

This patient presumably drank about three to four times the dose of methyl alcohol regarded as lethal. In addition, he drank large quantities of ethyl alcohol. It was amazing that a man who on admission to hospital was suffering from active pulmonary tuberculosis should have recovered from the poisoning completely.

#### Case 8.

Reference number 20665/41 — M. Th. J. A casual labourer, aged 34.

In the company of one of his friends, this patient had drunk »denatured spirits» bought in a colour shop. When admitted to hospital on December, 14, 1941, at 12.30 o'clock, he was unconscious, and his respiration was superficial and intermittent. He was much cyanosed, and there was scum about his mouth. His pulse was not palpable, and his dilated pupils were reactionless. The alkali reserve was 7.8 vol. per cent., and the blood contained 5.7 mg per cent. of formic acid. He died 40 minutes after admission to hospital. The necropsy showed subpleural ecchymoses, cyanosis of the organs and oedema of the lungs. Methyl alcohol was found in the stomach, blood and urine.

#### Case 9.

Reference number 2193/42 — L. M. H. A sausage-maker, aged 37.

Hitherto well, he shared on February 1, with two companions, a bottle of spirits (750 cm<sup>3</sup>) which one of them had bought at a very high price of a stranger. All three agreed that they had drunk the same amount of the spirits to which sugar and hot water had been added. On the following days the patient did not drink ethyl alcohol in any form.

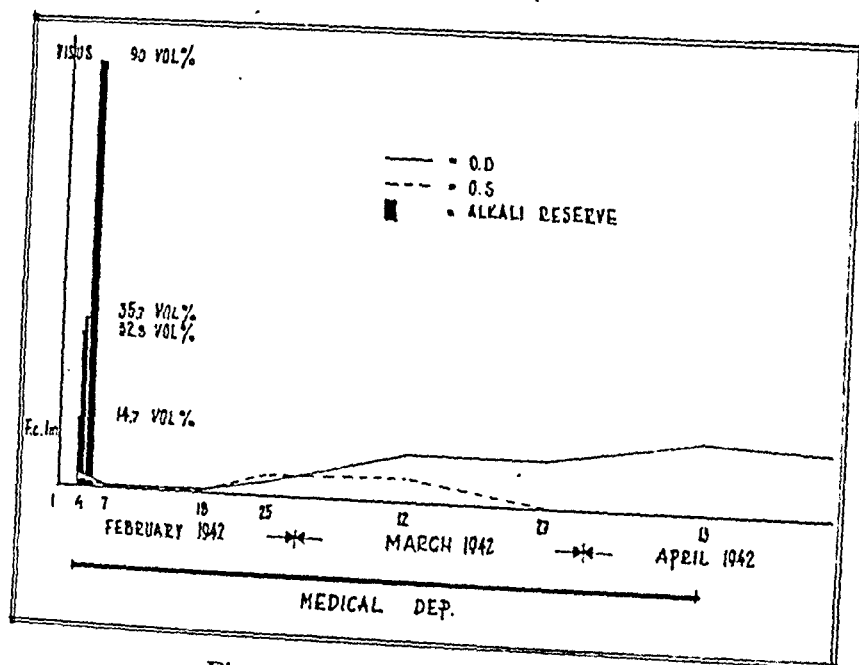
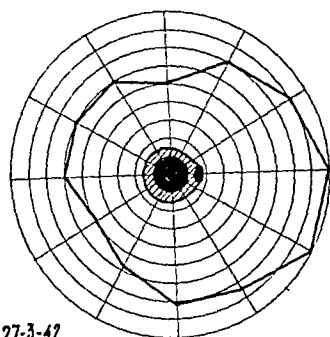
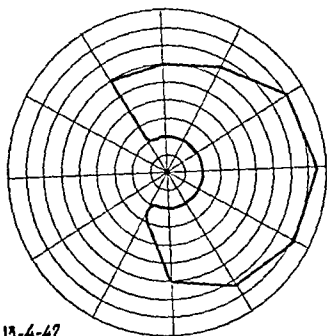


Fig. 10 — Case 9. — L. M. H.

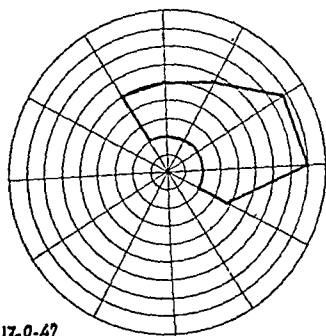
He worked as usual on February 2, but at 8 o'clock on February 3 he became limp and giddy, and therefore went home. At 20 o'clock he developed an intense headache and severe dyspnoea, with nausea and repeated vomiting. He suffered from photopsia, and during the night his vision failed rapidly.



27-3-42



15-4-42



17-9-42

O. D.

Fig. 11 — Case 9. — L. M. H. Size of objects 10/330 and 10/1150. No colour perception.

On admission to hospital on February 4, he was clear-headed, but loss of vision was almost complete. The pulse was 8, regular. The temperature was  $37.1^{\circ}$  C, and the blood pressure 160/95. Respiration very deep, frequency 18. A clinical and neurological examination showed nothing amiss apart from the eyes. A trace of albumin in the urine found at first was not demonstrable on the following days.

Alkali reserve at 9 o'clock 14.7 vol. per cent. At 12 o'clock 32.8 vol. per cent. At 15 o'clock 35.7 vol. per cent., and on February 5, 90 vol. per cent. Formic acid in the serum 7.2 mg per cent., in the urine 3.2 mg per cent.

On February 4, he was given an intravenous injection of 500 cm<sup>3</sup> of a 5 per cent. solution of NaHCO<sub>3</sub> in 1400 cm<sup>3</sup> of normal saline solution. NaHCO<sub>3</sub> 10 g  $\times$  4 by the mouth. On February, 5, NaHCO<sub>3</sub> 10 g  $\times$  4 by the mouth.

An ophthalmological examination showed normal externa and clear media. The pupils were round, 6 mm, reacting very feebly to light. The outlines of the injected optic discs were ill-defined, and there was some oedema at the centre of the fundus.

Vision O. s.: Movements of the hand 0.2 m. O. d.: Movements of the hand  $\frac{1}{2}$  m. Light projection uncertain on both sides, tension normal on both sides. The further course of the case is indicated on the chart.

Visual fields: See fig. 11.

On February 25, the colour of the optic discs and the appearance of the blood vessels were normal. On March 12, the right optic disc was a trifle pale in the temporal region, and the left was pale grey. The appearance of the blood vessels was normal.

On March 13, he was sent home, and on March 27, both optic discs were pale and the blood vessels atrophic. He was now blind on the left eye. On re-examination on September 17, vision of the right eye: Finger-counting  $\frac{3}{4}$  m. The field of vision more limited.

In the following case, the poisoning ran a much milder course.

#### Case 10.

Reference number 2192/42 — O. G. An electrician, aged 37.

This patient participated on February 1 with the last-mentioned person in the same spree, the same quantity of methyl alcohol-containing spirits being drunk by the two.

On February 2, about 15 o'clock, he suffered from nausea and vomiting, and pain in the limbs, stomach and kidney regions.

On February 3, he also suffered from nausea and vomiting, and his vision seemed a little cloudy. A third companion, O. H., who had not fallen ill, visited him on this day. Together they drank a bottle of «akevit» (750 cm<sup>3</sup> of 42 vol. per cent. of ethyl alcohol) and three bottles of «landsöl» — light beer — (2250 cm<sup>3</sup> of 2 vol. per cent. of ethyl alcohol). That evening he felt better than earlier in the day.

On February 4, he felt on the whole better than on the previous day, and he was free from pain, but he felt limp and drowsy. Having heard that one of his companions (patient nr. 9) had been admitted to hospital in a much exhausted state, he also wished to receive in-patient treatment.

On admission to hospital he had no other symptom than feeling limp. His pulse was 100, regular. His temperature was 37.4° C, his respiration unembarrassed. Normal findings on clinical examination and urine ana-

lysis. Alkali reserve 27 vol. per cent. An ophthalmological examination showed normal externa and clear media. The pupils measured 4 mm, reacting well to light and accommodation. The ill-defined optic discs were injected and a trifle oedematous. Vision 6/9 O. u. Satisfactory accommodation and normal limits of fields of vision and normal tension.

Treatment on February 4, —  $\text{NaHCO}_3$  10 g  $\times$  4 by the mouth, and on February 5,  $\text{NaHCO}_3$  10 g  $\times$  1.

On re-examination on February 19 and March 15, conditions were normal. Vision 6/6 o. u.

The person, who drank methyl alcohol-containing spirits with the last two patients, and who also drank «akevit» and beer with the last patient on February 3, experienced no discomfort after the poisoning. On the day after it (February 2) he consumed, together with another companion, a bottle of gin (750 cm<sup>3</sup> of 45 vol. per cent. of ethyl alcohol) as well as an unknown quantity of beer. He thus consumed large quantities of ethyl alcohol on both February 2 and 3. Also on February 4, he was seen notably drunk.

### Case 11.

Reference number 6641/42. — W. J. A storehouse clerk, aged 32.

Hitherto well. At 15 o'clock on April 12, a comrade appeared with half a bottle of spirits which was drunk by them and the patient's wife in the course of a few hours. He stated that he felt slightly tipsy. He slept well during the night, but felt limp next morning, suffering from nausea and unable to eat. At 10.30 o'clock he drank half a bottle of Pilsner beer, vomiting shortly afterwards. The vomiting did not recur, but the nausea persisted. About 13 o'clock he felt faint and drove home.

On admission to hospital on April 13, he seemed fit, but he complained of pressure over the eyes and feeling limp. His pulse was 80, regular. His temperature was 37.2° C, his blood pressure 105/65. Respiration unembarrassed. The pupils were equal, reacting well to light and accommodation. Normal findings on clinical examination and urine analysis. His stomach was washed out immediately after admission to hospital, and magnesia and charcoal were introduced through the stomach tube.

Alkali reserve on April 13 — 33.8 vol. per cent. Formic acid in the serum — 8.8 mg per cent., and in the urine 1.8 mg per cent. Alkali reserve on April 14 — 72 vol. per cent.

An ophthalmological examination showed normal externa. The pupils reacted well to light and accommodation. The limits of the optic discs were slightly blurred. Vision 6/6, the fields of vision normal. Tension X/12 (20 mm) on both sides.

He was given an intravenous injection of 300 cm<sup>3</sup> of a 5 per cent. solution of  $\text{NaHCO}_3$  plus 700 cm<sup>3</sup> of normal saline solution. On the same day,  $\text{NaHCO}_3$  10 g  $\times$  3, and on April 14,  $\text{NaHCO}_3$  15 g  $\times$  3 by the mouth.

On April 16, all was normal and vision was 6/6 on both sides.

On re-examination on October 5, the ophthalmological findings and vision were normal.

**Case 12.**

Reference number 6642/42 — I. J. A housewife, aged 32.

Previously well, she drank on April 12 together with her husband (case 11) and his companion about the same quantity of methyl alcohol each of them had taken. She did not become noticeably intoxicated, but next morning she felt giddy and unwell, vomiting once and suffering from nausea. Since then she had continued to feel unwell and giddy. She complained of shimmering, but not of any definite diminution of vision.

When examined on April 13, she felt limp but looked well. The pulse was 74, regular. The temperature was 36.9° C, and the respiration was 18, unembarrassed. The blood pressure was 120/75. The pupils were equal, reacting well to light and accommodation. There were no demonstrable disturbances of vision, and the clinical examination was negative. The trace of albumin found in the urine was not demonstrable on the following days.

April 13, alkali reserve 26.2 vol. per cent. April 14, 47 vol. per cent. April 15, 71 vol. per cent. Formic acid in the serum on April 13, 4.6 mg per cent., in the urine, 2.2 mg per cent.

The ophthalmological examination showed normal externa. The pupils were 4 mm, equal, reacting well to light and accommodation. The outlines of the optic discs were blurred. Vision was 6/6 on both sides, and the limits of the field of vision were normal (Donders). Tension on palpation normal.

On April 13, 300 cm<sup>3</sup> of NaHCO<sub>3</sub> 5 per cent. plus 700 cm<sup>3</sup> of normal saline solution were given by intravenous injection, and NaHCO<sub>3</sub> 15 g × 3 by the mouth. On April 14, NaHCO<sub>3</sub> 5 g × 4 by the mouth.

April 17, normal ophthalmological findings. She felt well and was discharged. October 5, the fundi and vision were normal.

**Case 13.**

Reference number 6683/42. — J. K. An engineer, aged 54.

In 1931, he had been treated at the Psychiatric Department for alcoholism. It seemed that in November 1941, he had drunk some methyl alcohol, and his vision had been defective for some time after. On April 12, he drank methyl alcohol together with the two preceding patients, according to whom he had probably drunk some of this alcohol on April 11 also.

On April 13, he was pale and looked ill, but he went to work. At 5 o'clock on April 14, he awoke with severe epigastric pain and violent vomiting. He complained of failing vision.

On admission to hospital at 8.15 o'clock on the same day, he was unconscious and cyanosed, in a cold sweat. The pulse was 60, weak but regular. The respiration was stertorous and irregular, but not rapid. The pupils were dilated, about 6 mm, reactionless. The clinical findings were otherwise normal.

Alkali reserve 16 vol. per cent. Formic acid in the blood 17 mg per cent., lactic acid in the blood 180 mg. per cent.

Death occurred at 9.10 o'clock, and the necropsy showed cyanosis of the organs, subpleural ecchymoses and purulent bronchitis.

**Case 14.**

Reference number 6682/42 — O. B. A printer, aged 40.

A friend stated that the patient had always drunk much alcohol, and had had access to methylated spirits at his place of work. Having started work on the morning of April 14, he walked out and fell down »blue in the face» and snoring. He was quite stiff, and he had, it was alleged, drunk an unknown liquor out of a bottle containing a white sediment.

On admission to hospital at 7.35 o'clock, he was comatose, and his stertorous respiration was of the Cheyne-Stokes type. His face was red-blue, and much mucus escaped from his mouth. There was general rigidity of the limbs with a few clonic contractions.

Pulse 100, regular. Blood pressure 130/60. Pupils dilated, about 6 mm. reacting very feebly to light. Clinical findings normal apart from albuminuria.

At 8 o'clock alkali reserve 19 vol. per cent. At 12 o'clock 86.2 vol. per cent. Lactic acid in the blood 170 mg per cent. Formic acid in the blood 3.5 mg per cent., and in the urine 5.2 mg per cent.

He was treated with 450 cm<sup>3</sup> of a 5 per cent. solution of sodium bicarbonate given by intravenous injection, supplemented by 30 g of the same drug introduced through a stomach tube.

An examination at 13 o'clock showed vertical nystagmus. The equal, 3.5 mm pupils reacted well to light and accommodation. The optic discs were injected, vision was 6/6 on both sides, accommodation was good, and the fields of vision were normal. On examination on April 23, the nystagmus had disappeared. Vision normal. The stomach contained methyl alcohol and pyridin.

In spite of his alarming state, the patient made a remarkably rapid recovery. The acidosis was quickly corrected by large quantities of sodium bicarbonate.

On re-examination on September 19, 1942, he stated that he had drunk of the same bottle on the evening before he fell ill. He had been very thirsty in the morning, and had taken another dose of methyl alcohol-containing spirits mixed with beer. The examination showed a normal ophthalmological picture and normal acuity of vision.

**Case 15.**

N. N. A postman, aged 24.

This patient, whose case has already been recorded by Dr J. F. Harboe (16) had hitherto been well, and his vision had been good. Said to be moderate in his consumption of tobacco and alcohol.

On August 5, 1919, he drank about one dessertspoonful of spirits mixed with four times as much water ostensibly for the cure of a cold. On the following day he went to work as usual, and at midday he suffered from headache, nausea and vomiting which did not, however, prevent his working till the end of the day.

On August 7, the above symptoms were supplemented by cloudiness of vision. On August 8, vision was considerably reduced, and the vomiting



continued. During the following days there was gradual improvement in the general condition, and during the last few days preceding his admission to hospital, his vision improved somewhat. He was admitted to hospital on August 13 when the fundi were seen to be normal. Vision as indicated on the following chart.

O. s.: Remaining part of field of vision between  $10^{\circ}$  and  $40^{\circ}$  in the temporal region. The field of vision gradually extended, and on September 2 its limits were normal, with a small relative central scotoma. O. d.: On August 14, a sector-shaped defect in the upper nasal region, the limits in other respects normal. On September 2, the limits were normal, with a central scotoma for red and green.

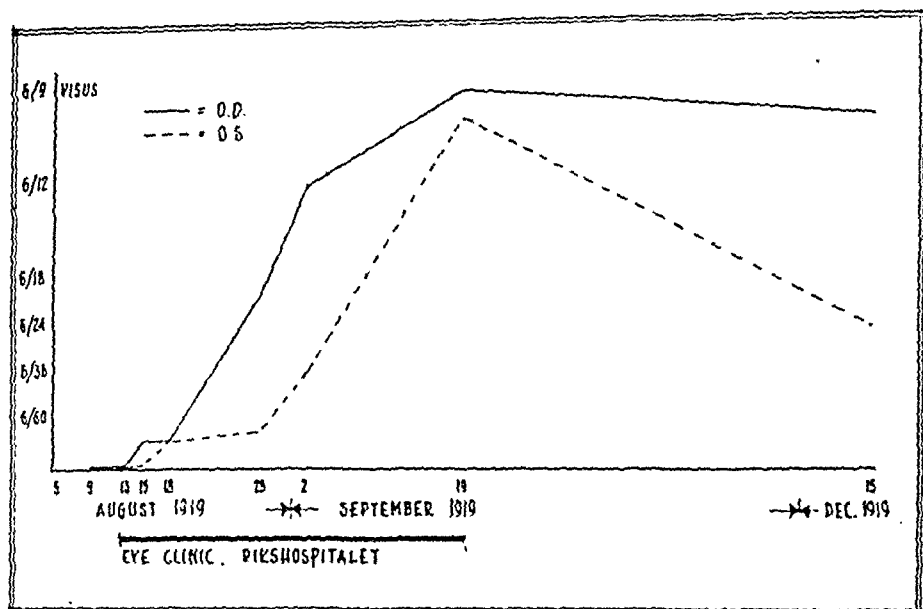


Fig. 12. — Case 15 — N. N. The chart is drafted according to Dr Harboe's description. After September 19, the scale of the absciss is only half what it was before this date in order to economize space.

On the patient's discharge from hospital on September 19, there were no definite changes in the fundi apart from some pallor of the left optic disc.

On re-examination on December 15, the pupils reacted a little more sluggishly than on discharge. The optic discs were now definitely paler than normal, particularly on the left side where the blood vessels were atrophic. He was red-green blind throughout the field of vision.

An analysis showed the spirits to be methyl alcohol.

Though this patient had, it would seem, drunk a very small quantity of methyl alcohol, the general symptoms were severe and vision was much reduced. His work was heavy, consisting of bicycling and walking up and down stairs all day as a postman.

## Case 16.

Reference number 12770/31 — O. K. A telegraph worker, aged 30.

This case has already been recorded by Ustvedt and Mohn (52). He was treated in 1927 at the Eye Department of the Rikshospital for an injury to his right eye whose vision had since been defective. In other respects he had been well.

On October 25, 1931, he drank some spirits which he had not bought himself but which, he was told, had been bought at the Wine Monopoly. Next day he felt well and continued at work till the evening. He drank

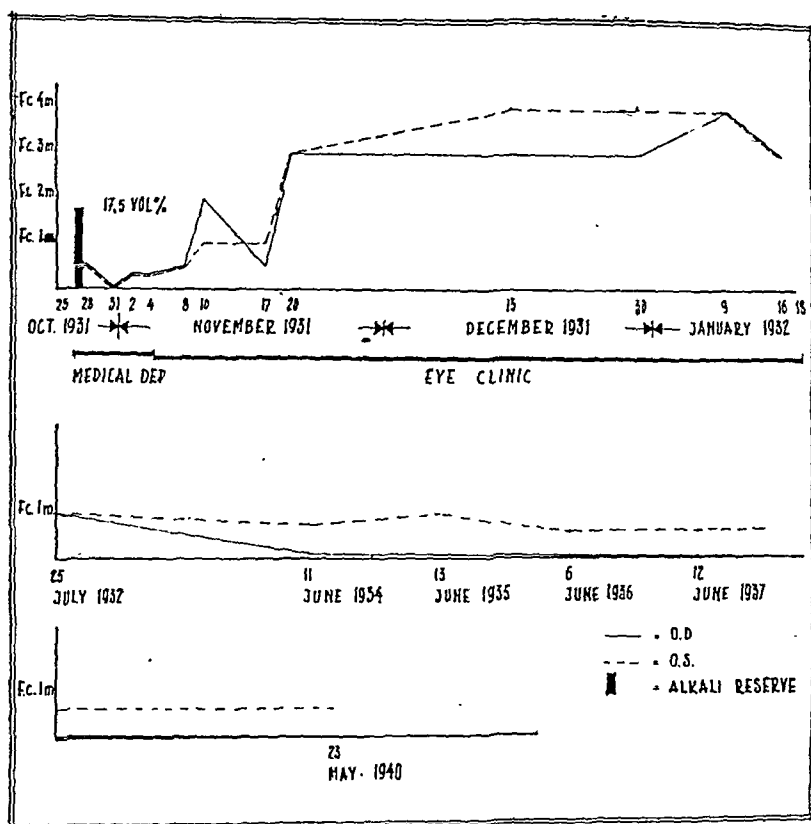


Fig. 13. — Case 16. O. K. The chart is drafted according to the account of Ustvedt and Mohn and notes from the hospital record.

some port wine in the afternoon. He vomited on the following night, and on the morning of October 27, his vision was cloudy when he went to work. Arrived at his destination, he vomited again and had to taxi home at 8.30 o'clock. His vision diminished rapidly in the course of the day. He was not fully conscious when he came to hospital.

On October 27, the brownish-yellow contents of the stomach, repeatedly vomited, were malodorous. His respiration was laboured, but his breath did not smell of acetone. He could see only movements of the hand. His pupils were dilated, reacting feebly to light. The right eye showed a

macula of the cornea and a coloboma of the iris. The clinical findings were normal.

Urine: Heller + Rothera ++ Gerhard ++ Schlesinger ++. A few granular casts, leucocytes and erythrocytes. Alkali reserve 17.5 vol per cent. Blood-sugar 120 mg per cent. Urea in total blood 70 mg per cent.

Five hours after admission, the patient was very drowsy, and his breath smelt faintly of acetone. An intravenous injection of 500 cm<sup>3</sup> of a 5 per cent. solution of glucose, and a drop-enema of 1 liter of a 3 per cent. solution of glucose were given. Methyl alcohol was found in the stomach and the blood.

On ophthalmological examination on October 28, the pupils were 6.5 mm, reactionsless. The optic discs were injected and their limits ill-defined. Movements of the hand  $\frac{1}{2}$  m on both sides.

The further course of the case is seen on the chart.

On his transfer on November 4 to the Eye Department, the limits of the field of vision were normal, but there was a large absolute central scotoma for white. Totally colour blind.

December 3: The optic discs, particularly the right, pale.

January 16: Both optic discs pale, the blood vessels atrophic.

For several years he came to the Eye Department to be re-examined and certified as unfit for work. As the chart shows, vision has diminished all the time, and his right eye is now blind.

It is obvious that, with so small a number of cases, the opportunities for drawing conclusions as to the pathogenesis and treatment of this form of poisoning are limited. It has, however, earlier been shown that clinical investigations, even of a single patient, have yielded valuable information as to the nature of the poisoning. There are thus grounds for recalling that the correctness of the findings of Harrop and Benedict (17) in a single case have been confirmed by later clinical experiences. It is, therefore, undoubtedly justifiable to seek in clinical investigations the key to the problem of methyl alcohol poisoning in man.

The conclusions drawn depend partly on observations on the cases just recorded, partly on the clinical observations and experimental findings of other workers.

## V. The Relation between Acidosis and Amblyopia.

In looking for the factors determining amblyopia, it is natural first to ascertain if there is any relationship between it and the general symptoms, — limpness, nausea, headache, dyspnoea, vomiting, pain in the muscles, — precisely the manifestations of acidosis.

Can we then establish any relationship between amblyopia and acidosis?

As many of the patients were admitted to hospital after their condition had improved, the determination of the bicarbonate content of the blood could not in these cases give any indication of the degree of the acidosis at the most acute stage of the poisoning. It is, therefore, of importance to recognize the clinical manifestations of acidosis in its various stages in order that the history of a given case may indicate the stage of acidosis at which disturbances of vision developed.

According to Kirk, (26) the clinical manifestations of the milder degrees of acidosis are, as a rule, lassitude, anorexia, nausea and headache. When the alkali reserve has fallen to the half of normal, the dyspnoea of acidosis develops and is at first regarded by the patient merely as functional dyspnoea. In the severe degree of acidosis, dyspnoea is more pronounced, and attacks of vomiting and pain in the muscles occur. In addition, sopor and coma often are present, but the development of the psychic disturbances depends not only on the degree of the acidosis, but also on other factors such as the degree of dehydration.

The alkali reserve was not determined in cases Nrs. 1 and 2. They were not admitted to medical wards on entering hospital as their consumption of methyl alcohol had not been admitted and they showed no general symptoms. One may, however, assume that both had suffered from severe acidosis before entering hospital, as the first had suffered from vomiting and dyspnoea, as well as being light-headed, and the second had been drowsy for two days. To judge by their clinical records, both these patients must have suffered from prolonged acidosis. They recovered but little of their sight and are now practically blind.

In case Nr. 5, the patient was admitted to hospital after the general symptoms had subsided. There was now a moderate degree of acidosis (27 vol. per cent.). Earlier he had shown signs of severe acidosis (vomiting and drowsiness) and they had lasted for at least a day and a half. On admission to hospital this patient's vision was almost nil, and afterwards he was blind for many days.

In case Nr. 15, the headache, nausea and vomiting lasted several days after the poisoning, and dimness of vision was observed after

they had lasted about 24 hours. Loss of vision was progressive during the following days, and there was only perception of light on the fourth day, after which vision improved. On and after the fourth day, there was a gradual improvement in the general symptoms.

In cases Nrs 4, 7, 8, 9, 13, 14 and 16, in which the patients were admitted to hospital during the most acute stage of the poisoning, the alkali reserve was respectively 9, 16.4, 7.8, 14.7, 16, 19, and 17.5 vol. per cent. In all these cases there were severe disturbances of vision as well as profound exhaustion. Cases Nrs 4, 8, and 13 ended in death. In the two first, the alkali reserve was remarkably low, 9 and 7.8 vol. per cent. respectively. It was 16 vol. per cent. in the third case which was, however, complicated by purulent bronchitis. This probably contributed to the fatal issue. In all three cases the pupils were dilated and reactionless.

In case Nr. 14, in which the patient was comatose on admission and the alkali reserve was 19 vol. per cent., the pupils were dilated, reacting feebly to light. There can be little doubt that the rapid correction of the acidosis saved this patient's life and sight.

In cases Nrs. 11 and 12, the general symptoms were slight and the degree of acidosis moderate, the alkali reserve being respectively 33.8 and 26.2 vol. per cent. The first patient had not noticed any disturbances of vision, whereas the second had noticed flimmering without any reduction of vision being demonstrable.

To judge by these cases, the degree of the amblyopia depended on the degree and duration of the acidosis. The disturbances of vision were not noted till such symptoms as nausea, vomiting and dyspnoea had lasted some time. It is, therefore, probable that failure of vision in these cases began when the degree of acidosis changed from moderate to severe. (About 23 vol. per cent.).

It might seem that case Nr. 3 was an exception, as there was severe amblyopia on the day on which the alkali reserve was found to be 26 vol. per cent. The blood test was, however, taken early in the morning. During this day, his condition became rapidly worse, and when his eyes were examined at 14 o'clock he suffered from very severe dyspnoea — typical Kussmaul's respiration — and such great restlessness that it was most difficult to examine him. At this stage he must, therefore, undoubtedly have been suffering from much more severe acidosis than earlier in the morning.

Cases Nrs. 1 and 6 are exceptions in so far as the disturbances of vision appeared before the general symptoms. The possible reasons for this will be discussed later.

Haskell and his associates (18), experimenting on dogs, have come to the conclusion that there is no causal relationship between the severity of the general symptoms and the degree of the acidosis. In their experiments large doses of methyl alcohol were given. Thus in their experiments Nrs. 16 and 23, the dosage of methyl alcohol per kilo body weight was 10 cm<sup>3</sup>, the dogs also being given 1 cg of morphine per kilo body weight. The dogs became profoundly comatose, dying in a short time without a low alkali reserve in the blood being observed.

It is a general experience that smaller quantities of ethyl alcohol than of methyl alcohol are needed to kill an experimental animal rapidly. This evidently depends on the narcosis, for the narcotic action of ethyl alcohol is greater than that of methyl alcohol because of the former's greater capacity to reduce surface tension in aqueous solutions (Warburg's narcosis theory). When, however, small doses are given repeatedly, the action of methyl alcohol is more toxic, whereas ethyl alcohol can be tolerated for a long time.

Clinical observations do not tally with these workers' experimental findings, and we are not justified in applying them to the reaction of human beings to methyl alcohol. For they never take such large doses that any appreciable degree of narcosis is induced. Usually such patients say they did not become intoxicated on drinking methyl alcohol.

*To judge by the clinical observations mentioned, the degree and duration of the acidosis would seem to determine the degree of the amblyopia. To throw further light on its pathogenesis, we must therefore find out how acidosis arises.*

## VI. The Mechanism of Acidosis.

Berens (2) says of the metabolism of the retina: »If, as seems likely, the retina and brain metabolism parallel each other, it could logically be stated that dextrose is the precursor of lactic acid which is probably the fuel of the living retina.» According to the same author, Adler found that the retina contains more carbohy-

drates and consumes them more rapidly than any other of the eye's tissues.

If we compare this with Goldschmidt's finding that methyl alcohol greatly reduces the tissue respiration of the retina, it seems natural to conclude that methyl alcohol induces inhibition of the processes of oxidation throughout the body, for glycolysis takes place in every cell.

Can the manifestations of the poisoning depend on the action of the methyl alcohol itself or on that of formaldehyde or on that of formic acid?

It is primarily Carlo Egg (9) who has maintained that methyl alcohol itself is responsible for the poisoning. He assumed that methyl alcohol forms a complex compound with the iron in the cells and thereby checks the processes of oxidation. In support of this view he pointed out that methyl alcohol checks *in vitro* many processes of oxidation, e. g. the guaiac and benzidin reactions, indigo oxidation, and the phenol reaction to  $H_2O_2$ . These reactions are also checked by ethyl alcohol, and the check to the last two reactions is greater than that effected by methyl alcohol.

If the check to the processes of oxidation in the body depends on the same processes in operation *in vitro* in the above mentioned reactions, it is impossible to explain away the fact that ethyl alcohol and methyl alcohol do not give rise to one and the same kind of poisoning. Egg's view can, therefore, hardly be correct.

In the opinion of many, formaldehyde is the active agent (Brückner, Flury and Wirth, Kazas).

The oxidation of methyl alcohol proceeds very slowly, and various investigations have shown that formaldehyde is present in the tissues only in very small quantities. Thus Pohl (35) could find it only in muscle, and here only in small quantities. Völtz and Dietrich (53) could not find it in the exhalation of dogs, although Keeser (cit. 20) found it in the distillation of animals.

Brückner (6) considers that formaldehyde acts by reacting with the protein molecules. A formol reaction, with the formation of methylenimin derivatives possessing acid properties, must be considered as a possibility. Only part of the formaldehyde can, however, be altered in this fashion, for this reaction is not quantitative till  $pH = 9$  is reached. The resulting acid products can exist

only in very small quantities, and the acidosis cannot be explained as a result of them.

Pohl, who assumed that the specific toxic action of methyl alcohol depends on the formic acid produced, has shown experimentally that, as a rule, the peak of excretion was reached on the third and fourth day after the poisoning, and that at this stage the experimental animals suffered most. He found from 5.8 to 18 per cent. excreted when he gave the animals between 1 and 2 g of sodium formiate. Hence his conclusion that most of the formic acid is converted into carbon dioxide and water. Asser (1) found after a dose of 2 g of formiate, 15 to 20 per cent. excreted in the urine. Schmiedeberg considered that the acidosis demonstrated in the patients in the mass outbreak of methyl alcohol poisoning in Berlin in 1911—1912 depended on formic acid in the same way that the acidosis of diabetes depends on beta-oxy and beta-keto butyric acid. He evidently thought that formic acid was present in such large quantities that it could induce acidosis by binding alkalis.

This view would not seem to be correct. Because the oxidation of methyl alcohol is slow, and because most of the formic acid is converted into carbon dioxide and water, the quantity of this acid in the body cannot be great enough to account for the acidosis. In certain cases very small quantities of methyl alcohol induce severe acidosis.

In those cases of the present study in which the concentration of formic acid in the blood was investigated, the highest figure was 19 mg per cent., or 4.13 millimol (case Nr. 4). In this case the plasma bicarbonates were 3.91 millimol (9 vol. per cent.) as compared with the normal 26. This enormous reduction can, therefore, not have been due to formic acid alone.

*Another possible effect of formic acid, hitherto apparently overlooked, may be mentioned here.*

One of the qualitative tests for demonstrating formic acid is the colour reaction it gives rise to with iron chloride. According to Gmelin (12), when sodium formiate and iron chloride are mixed, a compound of iron and formic acid is formed. In this compound, the iron is bound in complex fashion both in the kat-ion and the an-ion. Another complex compound is sodium-ferri-formiate.  $\text{Na}_3[\text{Fe}(\text{COOH})_6]$ .



According to the theory of Warburg (Langfeldt 28) concerning the oxygen activation in the cells, whatever reacts with iron may disturb the transmission of oxygen provided that the substance in question can penetrate into the cells, and that its affinity for iron is so great that it can dissolve its natural compounds. Even if one cannot without more ado assume that formic acid reacts as easily to the iron in the pyrrols in the respiratory enzyme as to ionized iron, the possibility may yet exist that formic acid may form a complex compound with iron also in the body. The formic acid would thereby come to act like prussic acid, with this difference only that the affinity of the latter for iron would seem to be much greater.

According to Poulsson (38) the minimum lethal dose of HCN is 0.06 g. As 0.10 g of HCOOH can bind as much iron as the quantity of HCN mentioned, it is difficult to accept the opinion of Egg (9) who maintained that the quantities of formic acid in the body are too small to hurt it.

It is also impossible to agree with Flury and Wirth (10) in their opinion that the formiate ion is harmless.

Discussing the oxidation of methyl alcohol in the body, Pohl has written: »Die geringere Oxydirbarkeit des Methylalkohols gegenüber dem ihm homologen Aethyl-alkohol kann nach obigem darin ihre vorläufige Erklärung finden, dass der Körper die bei letzterem intermediär gebildete Essigsäure selbst in grossen Mengen noch zu zersetzen vermag, während er für die Formiate nur ein bald erschöpftes Oxydationsvermögen besitzt.»

This observation is the more remarkable for the fact that formic acid is very easily oxidized in vitro, whereas the reverse is the case with acetic acid.

The gradually diminishing capacity of the organism to oxidize formic acid can, however, apparently be explained by the assumption that it forms a complex compound with the iron in the respiration enzyme (cytochrom-oxydase). The processes of oxidation in the cells will thereby be gradually inhibited, and this reduced capacity for oxidation will also affect the oxidation of formic acid formed as long as methyl alcohol is present in the body. The concentration of formic acid in the tissues will then increase, and this in its turn will bind more iron.

According to this theory of the processes of acidosis, one would

expect to find an increase of organic acids, notably lactic acid, in the blood and urine. Several earlier investigations would seem to show that this is the case.

Krohl (27) found that the excretion of ammonia in the urine was very great in proportion to the excretion of formic acid. He did not ascertain which was the acid that had neutralized the bulk of the ammonia.

Harrop and Benedict (17) demonstrated large quantities of titratable organic acids, mainly lactic acid, in the urine.

In a case of methyl alcohol poisoning investigated by Ustvedt (51), the difference between the total base and the total acid was 30.15 mille-equivalents — an observation indicative of large quantities of organic acids in the blood. He indicated the possibility of an increased lactic acid concentration in the blood, but he did not demonstrate it.

This state was demonstrated in cases Nrs. 13 and 14, the lactic acid concentration in the blood being found to be respectively 180 and 170 mg per cent. (the normal is 10 to 20 mg per cent. when the patient is at rest both before and during the withdrawal of blood).

This proves that the reduction of the bicarbonates in the blood plasma depends in the main on lactic acid. *The factor primarily responsible for the acidosis would seem to be formic acid.*

## VII. Factors Influencing the Degree of Acidosis.

### A. *The Influence of Increased Metabolism on the Acidosis.*

If the processes of oxidation are checked, no unqualified parallelism can be expected between the dose of the poison and the degree of the acidosis.

In cases Nrs 13 and 14, the lactic acid in the blood was found, as already mentioned, to be respectively 180 and 170 mg per cent. In the first of these cases, 17 mg per cent. formic acid was found in the blood, and the alkali reserve was 16 vol. per cent. In case Nr. 14 the figures were respectively 3.5 mg per cent. and 19 vol. per cent.

In spite of the great difference in the concentration of formic acid in the blood of these two patients, the difference between the lactic acid concentration and the alkali reserve was small. The first patient fell suddenly ill at 5 o'clock when he was awoken by violent

vomiting and pain in the abdomen. The other lost consciousness and fell while at work.

Two patients were admitted to the Drammen hospital on November 18, 1941, having drunk methyl alcohol-containing spirits. The one — A. J. — who had drunk more methyl alcohol than the other, was not fit to work on the day after the spree, being able to eat, but suffering from nausea and giddiness. He was light-headed at intervals, but felt better after resting. On the morning of November 18, he felt quite well, but he again was light-headed after he had been up and about for some time. His vision was slightly cloudy, but he noticed no breathlessness.

On his admission to hospital on the evening of the same day the methyl alcohol content of the blood was 0.075 per cent., and the alkali reserve was 22.3 vol. per cent. On ophthalmological examination (H. Gjessing, M. D.) the fundi were found to be normal. Vision O. s.: 5/5, o. d.: 5/9. A relative central scotoma for colours.

The other patient — B. J. — did heavy work on November 17. In the evening he was tired and giddy, and he noticed slight cloudiness of vision and a little dyspnoea, but he could eat as usual. Next morning there were no symptoms, and he went to work again.

On his admission to hospital the methyl alcohol content of the blood was 0.024 per cent. and the alkali reserve was 24.1 vol. per cent. The ophthalmological examination (H. Gjessing, M. D.) showed normal fundi. Vision o. s.: 5/5, o. d.: 5/8.

Though the quantity of methyl alcohol in the blood of this patient was barely one-third that of the first patient, the alkali reserve was almost equally low in both. This may have been so because the second patient had been at work, whereas the first patient had kept at rest, spending part of his time in bed.

What is also remarkable is the severity of the symptoms in case Nr. 15 when compared with the smallness of the quantity of methyl alcohol he was supposed to have drunk. This patient also did heavy work on the day after the poisoning.

Lewis Ziegler (57) has recommended thyroid extract for methyl alcohol poisoning. This seems irrational as acidosis increases with the increase of metabolism.

*Other things being equal, the acidosis must become more severe and the clinical picture correspondingly more alarming if great demands are made on oxidation.*

### B. *The Influence of Ethyl Alcohol on the Acidosis.*

As some patients drink ethyl alcohol just before, or on the days following, methyl alcohol poisoning, it would be interesting to learn how, if at all, its course is influenced thereby.

As a rule, the exact quantity of methyl alcohol consumed is not known, but in some cases it is stated that several persons in the same party had drunk the same amount of methyl alcohol-containing spirits. By comparing the course of the poisoning in those patients who had also drunk ethyl alcohol with that of the patients who had not done so, some clue as to the action of ethyl alcohol on methyl alcohol poisoning should be found.

In cases Nrs. 9 and 10, the two patients and a friend of theirs (O. H.) drank on February 1 equal quantities of methyl alcohol-containing spirits according to the statements of all three. The first patient came to hospital on February 4 with severe symptoms, an alkali reserve of 14.7 vol. per cent. and much reduced vision. He had not drunk ethyl alcohol.

The second patient, admitted to hospital on the same day, was much less seriously ill. The alkali reserve was 27 vol. per cent., and his slight disturbances of vision passed off rapidly. On the day before admission, i. e. February 3, he had shared with O. H. a bottle of «akevit» (750 cm<sup>3</sup> 42 vol. per cent. of ethyl alcohol) and 3 bottles of light beer (2250 cm<sup>3</sup> 2 per cent. of ethyl alcohol) in the course of the afternoon. Each of these two had therefore consumed about 180 cm<sup>3</sup> of pure ethyl alcohol on this day.

O. H., who had been used to drinking alcohol almost daily, had also drunk heavily on the day after the poisoning (February 2.). With another of his friends he had drunk a bottle of gin (750 cm<sup>3</sup>, 45 vol. per cent. of ethyl alcohol) and had also drunk an unknown quantity of beer. He had thus drunk at least 170 cm<sup>3</sup> of pure ethyl alcohol on this day. This person suffered no ill effects from the poisoning.

In case Nr. 3, the patient stated that he had drunk less methyl alcohol than the other three, and this statement was confirmed later by the two who recovered completely. Unlike his boon companions, this patient had not drunk ethyl alcohol either before or after drinking methyl alcohol.

A sister of the patient who died stated that he had remained at home on the day after the spree, and had not drunk alcohol.

The two who recovered completely from the poisoning drank a considerable quantity of alcohol the first two days after the poisoning.

In case Nr. 7, the patient stated that he had drunk in the course of two days about 300 cm<sup>3</sup> of pure methyl alcohol, i. e. many times the fatal dose which, according to Poulsson (38), is about 50—75 g. On the second day, when he began to feel ill, the patient drank five glasses of port wine (about 300 cm<sup>3</sup> 18 vol. per cent. of ethyl alcohol). On the morning of the third day, he drank a tumblerful of gin (about 150 cm<sup>3</sup> 45 vol. per cent. of ethyl alcohol), as well as some concentrated alcohol in an equal quantity of coffee. He could not say how much he had drunk of this mixture. But it is certain that he drank altogether considerable quantities of ethyl alcohol. Yet there were no permanent ill effects from the poisoning.

The observation that ethyl alcohol is an antidote to methyl alcohol is apparently supported by some experiments by Asser (1). He found that less formic acid was excreted in the urine of dogs given ethyl alcohol together with methyl alcohol than in the controls given methyl alcohol alone. Amyl alcohol and acetone influenced the excretion of formic acid in the same way.

Asser envisaged three possible explanations of this phenomenon:

- a) increased oxidation of  $\text{HCOOH}$
- b) reduced formation of  $\text{HCOOH}$
- c) a change in the mode of oxidation of methyl alcohol.

Accordingly he investigated the action of ethyl alcohol, amyl alcohol and acetone on the excretion of formic acid after the administration of 2 g of sodium formiate, and he found that less was excreted than when the same quantity of formiate was given alone. Hence his conclusion that an increased oxidation of formic acid was also the cause of the diminished excretion observed in the first experiments in which ethyl alcohol, amyl alcohol and acetone was given at the same time as the methyl alcohol.

The oxidation of the formiate must depend on the degree of its penetration into the cells, and alcohol may be assumed to make the cell membranes more permeable for the formiate.

This experiment does not prove that ethyl alcohol promotes oxidation of the formic acid in methyl alcohol poisoning when the formation of this acid is intracellular.

Probably the reduction in the excretion of formic acid effected by ethyl alcohol in methyl alcohol poisoning is due to a reduced formation of this acid. The following is an attempt to find a theoretical basis for this hypothesis.

According to Traube's rule, ethyl alcohol reduces the surface tension of aqueous solutions more than methyl alcohol, and Livingstone and his associates (30) have found this difference to be in the ratio of two to one.

Ethyl alcohol will therefore loosen the adsorption of methyl alcohol to the respiration enzyme, thereby checking its oxidation to formic acid.

The protection given by a single dose of ethyl alcohol will be limited to the time taken to oxidize it, and the manifestations of methyl alcohol poisoning may develop after this time. But during it, some of the methyl alcohol will, however, be excreted. According to Völtz and Dietrich (53), about one-quarter of the methyl alcohol given was excreted during the first two days, mainly by the lungs. A patient who has drunk ethyl alcohol will therefore be exposed to the action of a smaller quantity of methyl alcohol than would otherwise have been the case. If ethyl alcohol is taken repeatedly, there may be no signs whatever of poisoning in spite of large quantities of methyl alcohol having been taken.

One might expect a recurrence of the acidosis when the ethyl alcohol was oxidized, and this would seem to have been so in case Nr. 7. On the morning of the second day in hospital, the alkali reserve had risen to 44 vol. per cent. At this stage the methyl alcohol in the blood was 0.14 per cent. On the third day, the alkali reserve had again fallen to 31 vol. per cent. in spite of the administration of bicarbonate.

A chronic drunkard does not seem to be less predisposed than others to the action of methyl alcohol if he omits to drink ethyl alcohol when poisoned by methyl alcohol. Case Nr. 5 demonstrates this point.

It may be assumed from the above investigations that ethyl alcohol has a favourable effect on methyl alcohol poisoning. *The explanation of this must primarily be found in the capacity ethyl alcohol*

possesses to displace methyl alcohol from the inner surfaces of cells, its oxidation to formic acid being thereby checked. Nor can one neglect the capacity of ethyl alcohol to reduce metabolism as a factor influencing the course of the poisoning favourably.

### C. The Influence of the Supply of Much Fluid on the Acidosis.

Völtz and Dietrich (53) found that while under normal conditions only about 1.5 per cent. of the methyl alcohol taken is excreted in the urine, up to 15 per cent. may be so when diuresis is much increased.

Pohl (36) found that the quantity of formic acid excreted rose with the intravenous injection of normal saline solution.

The favourable course of the poisoning in case Nr. 10, may partly have been due to the large intake of fluid, and the same observation applies to this patient's companion, O. H., and to the two persons who drank methyl alcohol with the patient in case Nr. 3, for they had drunk much beer as well as more concentrated ethyl alcohol. In case Nr. 7, in which no beer was drunk, the supply of fluid can hardly have affected the issue appreciably.

One of the most constant manifestations of acidosis is dehydration of the organism which is increased by frequent vomiting. The relationship between the amount of fluid taken and the diuresis on the first day in hospital in some of the cases in which these items were recorded can be seen in the following table:

| Case | Supply of Fluid | Diuresis | Chlorides in Blood Plasma |
|------|-----------------|----------|---------------------------|
| 7    | 2600            | 1700     | 337 mg per cent.          |
| 9    | 4750            | 2100     |                           |
| 10   | 5685            | 900      | 282 " " "                 |
| 11   | 3800            | 950      | 323 " " "                 |
| 12   | 2400            | 800      |                           |

As this table shows, the quantity of urine was small in spite of a considerable intake of fluid. It must therefore be abundant if diuresis is to be profuse.

### VIII. The Pathogenesis of Amblyopia.

#### A. *The Possibility of a Causal Relationship of Acidosis to Amblyopia.*

As already mentioned, all the patients with severe acidosis suffered from serious visual disturbances which developed, as a rule, after the general manifestations of the poisoning had lasted some time. In two cases of moderate acidosis — about 30 vol. per cent. — in which there had been no signs of severe acidosis before admission to hospital, diminution of vision was not demonstrable.

In the three cases ending in death, the pupils were dilated and did not react to light.

A relationship having thus been established between the degree of the acidosis and the amblyopia, one may ask whether the former may be a contributory cause of the latter.

It may be noted in support of this hypothesis that a similar degeneration of the retina is quite often observed in several conditions associated with acidosis. It is not surprising, after what has already been said of the check to cell-respiration in this form of poisoning, that similar amblyopia occurs in cases of formalin and carbon monoxide poisoning. It is remarkable that the amblyopia of diabetes is always associated with acidosis, as emphasized by Rönne, Holth and others. Among other diseases which are apt to favour acidosis, and in which degeneration of the retina also occurs, may be mentioned the toxæmia of pregnancy, the cachexia of cancer, and extensive burns of the skin. In experimental thyreoidin poisoning, degeneration of the retina with secondary optic atrophy has been observed. Occasionally amblyopia follows loss of blood, nearly always in persons already very debilitated (Røe, 40). Acidosis may also occur in such cases, and its degree depends not only on the severity of the hæmorrhage, but also on other factors, notably the state of the heart (Jervell).

It is remarkable that in several cases blindness has followed venesection of patients suffering from cholera which is often associated with severe acidosis.

Considering that the metabolism of the retina is more lively than that of any other normal tissue, it seems reasonable to suppose that the reduction of the buffer capacity of the bicarbonates, phosphates and proteins provoked by the acidosis may injure the retina



more easily than other structures. One may therefore assume that the acidosis injures the retina by virtue of an increase in the hydrogen ion concentration.

This does not, however, explain the fact that the amblyopia of methyl alcohol poisoning is, as a rule, much more severe than that of the above mentioned morbid conditions.

The marked predilection shown by methyl alcohol for the retina in comparison with all other tissues can hardly be due to a greater accumulation of the alcohol in the retina. According to Pohl (37) Nicloux has not found any marked difference in the concentration of methyl alcohol in the various organs, and Pohl himself has found less of it in the cerebrum than elsewhere. Yant and Schrenck (55) found that, when methyl alcohol was inhaled by dogs, and its concentration in the blood was put at 100, its percentage distribution elsewhere was as follows:

|                                      |      |           |
|--------------------------------------|------|-----------|
| Contents of the stomach .....        | 103  | per cent. |
| Aqueous humour and corpus vitreum .. | 93.9 | » »       |
| Heart muscle .....                   | 84   | » »       |
| Hemispheres of the cerebrum .....    | 86   | » »       |
| Kidneys .....                        | 95   | » »       |
| Urine .....                          | 108  | » »       |

The concentration of methyl alcohol in bone marrow and fat was low. They came to the conclusion that the concentration of methyl alcohol is practically the same in all the tissues and cells in relation to their water content. We must, therefore, seek other explanations for the markedly selective action of methyl alcohol on the retina.

In the higher animals, Otto Warburg has shown that the retina has, as compared with other organs, a much greater consumption of oxygen in relation to its iron content, i. e. 100,000 mm<sup>3</sup> of O<sub>2</sub> calculated per milligram of iron per hour.

*The explanation of this selective action on the retina is, I believe, to be found precisely in what has just been said and in connexion with the severe acidosis. When the iron in the respiration enzyme is paralyzed, defective oxygen activation must occur earlier in the retina than in other organs.*

### B. *The Part Played by Light in the Pathogenesis of Amblyopia.*

In this study there are two patients whose vision declined before the general symptoms occurred, i. e. at a time when the acidosis must have been slight or moderate. In both these cases the eyes were exposed to strong light.

In case Nr. 1, the patient noticed diminution of vision when he was by the sea on a sunny day. All the three observations made

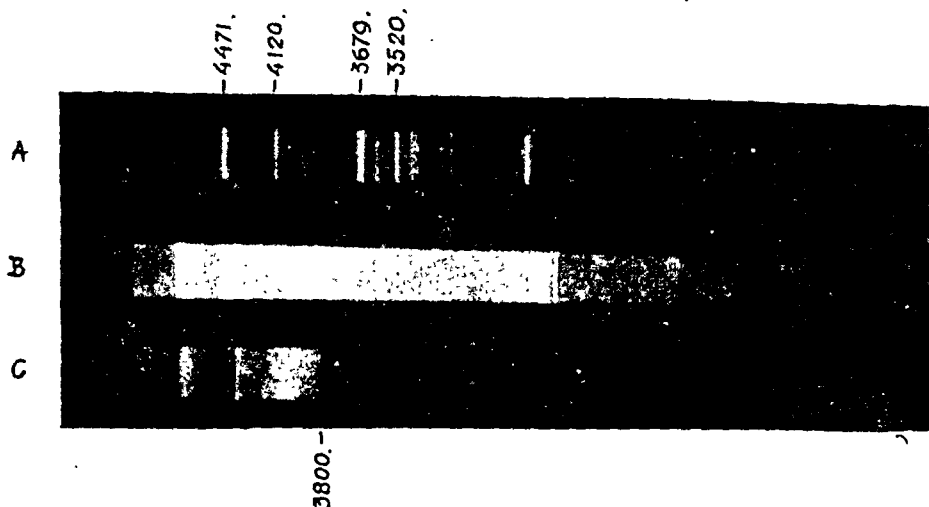


Fig. 14. A: Neon light. B: Autogen light, duration of exposure 16 seconds. C: Autogen light with filter, duration of exposure 16 minutes.

by the Meteorological Institute on this day confirmed this point. The patient's eyes must have been exposed to much light, both directly and by reflexion from the surface of the water. General symptoms appeared some hours later.

In case Nr. 6, the diminution of vision followed the exposure of the eyes to autogen light. The patient wore the protective spectacles he was accustomed to use. Their green glass was about 2 mm thick, and the spectacles fitted so as to shut out all light round the eyes.

Schanz (46) has maintained that the ultraviolet rays injure the retina in this form of poisoning. This is improbable, for under ordinary conditions the rays in question are absorbed by the refraction media of the eye.

Autogen light is very rich in active rays, and it would be interesting to learn how much of them could penetrate the glass of the

spectacles in question. This problem has been studied by Cand. Real. Frans Aubert at the University Physical Institute, Oslo. As the photo shows, no rays with a shorter wave-length than 3800 Ångström penetrated the glass even after prolonged exposure.

On the assumption that the amblyopia is due to inhibition of the processes of oxidation, the injurious action of light would naturally seem to depend on the increased calls on oxidation evoked by the visible rays of the spectrum.

According to Sattler (45), Schwarzkopf found no differences in the degree of the degenerative changes in the retinas of both eyes of animals poisoned with methyl alcohol when only one eye was exposed to light. This observation cannot forthwith be accepted as proving that light plays no part here. When poisoning is severe, the changes in the retina may attain the maximum limit independently of light. Further, when only one eye is illuminated, there will, to a certain extent, be increased glycolysis in the other, witness the observation that the cones in the retina contract even when only one eye is exposed to light (Fuchs).

When death occurs during the acute stage of poisoning, the degenerative changes in the retina are not limited to any definite part of it (Pick & Bielschowsky, Birch-Hirschfeld). The last-named made a point of insisting that the appearance of the central area and its immediate neighbourhood does not differ from that of the peripheral parts of the retina. The degeneration of the medullary sheaths of the optic nerve is no more prominent in the macula-papillary fibre bundle than in the other parts of the nerve.

This runs counter to the general opinion that these fibres are primarily most injured by methyl alcohol. It may be assumed that the central part of the retina later on shows the greatest loss of function and degenerates to a greater degree than the peripheral parts because of the great claims made by light on the processes of oxidation in the former.

As illumination of the retina increases the formation of lactic acid in it, and as oxidation and thereby also resynthesis are inhibited, the hydrogen ion concentration will increase. This is probably why severe amblyopia may occur even during a slight degree of acidosis if the eyes are exposed to strong light as in the case of the last two patients.

### C. *The Causes of the Characteristic Course of Amblyopia.*

It may seem strange that vision improves gradually even after prolonged amaurosis, but this tallies with the findings of Goldschneider and Flatau who, — according to Birch-Hirschfeld (4) — have shown that definite structural damage to the ganglion cells can be repaired. The last-named worker found in cases of methyl alcohol poisoning that the nuclei of the ganglion cells retained their normal structure for a remarkably long time. This may explain the tendency to undergo repair shown by the cells in question.

It may seem more difficult to understand the secondary failure of vision.

This failure began from six to 12 weeks after the poisoning in the patients whose amblyopia persisted and who were periodically re-examined. It is not till this stage is reached that definite pallor of the optic discs is, as a rule, observed; and in two cases (Nrs. 3 and 6) there was at the same time marked irregularity of the calibre of the larger blood vessels with thickening of their walls. These changes resemble those seen in the blood vessels of the retina in arteriosclerosis. It is not till later on that thin, atrophic blood vessels are seen.

The latest changes in the blood vessels were seen in case Nr. 6 in which the failure of vision was least. In the left eye, in which the diminution of vision began earlier than on the right side, the changes in the blood vessels were also detected earlier.

In case Nr. 9, in which the poisoning was very severe, the diminution of vision of the left eye began already after the sixth week when the optic disc was pale, whereas there were no definite changes visible in the large blood vessels. The optic disc on the right side was pale eight weeks after the poisoning, and when, two weeks later, he was re-examined, there was considerable limitation of the field of vision (Fig. 11).

There would thus seem to be a causal relationship between the degree of the amblyopia and the length of the interval preceding the onset of diminution of vision, and about the same time changes in the blood vessels (pallor of the optic discs and calibre variations) are seen.

As it must be assumed that the oxidation capacity of the degenerated cells is reduced, the eyes of these patients must be pro-

ected against strong light even after the acute stage of the poisoning. This precaution should delay failure of vision. According to Settler (45) Schieck has observed strikingly rapid failure of vision, after it had again become quite good, in a patient whose eyes had been exposed to strong sunlight.

Patients do not object to wearing dark glasses as they find that they often see better in weak than in strong light, — a phenomenon often observed in tobacco and alcohol amblyopia (Fuchs). The rapid failure of vision accompanying high fever in case Nr. 5 was striking. These observations can be explained as a sequel to the reduced oxidation capacity of the cells of the retina.

In some of these cases of amblyopia, the patients have traced failing vision to severe muscular exertion, and records of such cases are to be found in the literature (Wood and Buller). It is natural to explain this phenomenon as a result of the decreased buffer capacity which is induced by the formation of lactic acid during muscular exertion.

A secondary decline of vision was observed in this study in all the cases in which the amblyopia persisted. *This decline, and the gradually developing limitation of the field of vision, are presumably due to atrophy of the blood vessels. Strong light, fever and muscular exertion can hasten this decline.*

## IX. The Treatment of Amblyopia.

The treatment of amblyopia must consist of the rapid correction of the acidosis, the supply of large quantities of fluid, and the protection of the eyes against light. The most rational way in which to correct the acidosis is to administer an isotonic (1.3 per cent.) solution of sodium bicarbonate, the total dose of which should be calculated according to Van Slyke's nomogram.

It is not necessary to give the whole of this dose at the outset of treatment, but in every case one should aim at reducing acidosis from a severe to a moderate degree, i. e. the bicarbonate content of the plasma should be raised to 12—14 millimol (Kirk), a figure corresponding to an alkali reserve of about 30 vol. per cent.

For an intravenous injection it is sufficient to use solutions of the best quality of powdered sodium bicarbonate in sterilized water without any special sterilization of the powder itself (Kirk).

As the acidosis of methyl alcohol poisoning can recur rapidly, the alkali reserve should be investigated frequently during the early stages of hospital treatment, and the dosage of the bicarbonate regulated accordingly.

As Jervell (23) has shown, treatment with the bicarbonate increases the excretion of lactic acid in the urine. Probably the same is the case with formic acid.

In the absence of serious cardiac complications, the injection can be given at the rate of 1 litre per 10—15 minutes (Kirk). In several cases there were electro-cardiographic signs of myopathic changes. These signs, which disappeared in a few days, do not contra-indicate the treatment, though a certain cautiousness should be shown in the timing of the injection.

Even if the alkali reserve cannot be determined, it is safe to give a couple of litres of this solution provided there are definite clinical signs of acidosis. In addition, the bicarbonate should be given by the mouth until the reaction of the urine becomes alkaline.

As a supplement to this treatment of acidosis, it may be convenient to give ethyl alcohol so as to check the oxidation of methyl alcohol. This measure is of special importance when it is impossible to give an intravenous injection of the bicarbonate in adequate doses, as, for example, during prolonged transport to hospital. But the dosage of alcohol must not be such as to raise its concentration in the blood to more than 0.1 to 0.2 per cent. Later on, the amount of alcohol given should correspond to the amount oxidized (about 7 g per hour).

Profuse diuresis may be obtained by giving normal saline solution which corrects any hypochloraemia present. As, according to Völtz and Dietrich (53), methyl alcohol behaves like ethyl alcohol and acetone in being re-absorbed from the bladder, care must be taken to keep it always empty.

Gastric lavage is indicated as Yant and Schrenck (55) have shown that methyl alcohol is excreted into the stomach. As they have found that the concentration of methyl alcohol in the gastric juice is slightly higher than that in the blood, such treatment cannot be expected to remove much methyl alcohol. It does not, for that matter, constitute any immediate danger for the patient, *and gastric lavage should therefore not be carried out before, but after, an intravenous injection of bicarbonate.*

The above considerations point to the treatment being carried out on the medical side of a hospital during the acute stage of the poisoning, even in the cases in which the clinical signs of acidosis have disappeared on the patient's admission.

The eyes must be protected against light, particularly during the acute stage, but also later on if there is amblyopia.

Lewis Ziegler (57) recommends sweat baths and thyroid extract. Both are contra-indicated for reasons already mentioned.

Lumbar puncture is said by some (Pincus, Zethelius and Wersén) to influence the course of the amblyopia favourably. But as, under ordinary conditions, there is gradual improvement during the first few weeks, it does not necessarily follow that it is due to this treatment. The observation period was too short, only 1—2 months, to warrant drawing conclusions as to the final results. In most of the cases observed by these writers, the cerebro-spinal fluid was normal, and only in a few cases was the pressure slightly raised (between 150 and 200 mm H<sub>2</sub>O).

It was particularly in their sixth case that Zethelius and Wersén noted an apparently favourable reaction to lumbar puncture. Just before he noticed diminution of vision, the patient had drunk ordinary alcohol and thereupon half a tumbler of spirits whose taste was queer. Half an hour later he noticed diminution of vision. These writers evidently jumped to the conclusion that this last beverage was wood spirits, and that it was responsible for the rapid development of amblyopia. They must surely have been mistaken to judge by the common experience concerning the latent period of methyl alcohol poisoning. It is probable that in this case the methyl alcohol had been drunk at an earlier stage, possibly the day before. The large quantity of ordinary alcohol consumed may well have contributed to the favourable outcome of this case.

Schieck (48), who saw no benefit follow lumbar puncture in three cases, is not impressed by the favourable results claimed by these writers for this treatment.

## X. Conclusions.

### A. Pathogenesis.

1. The action of methyl alcohol is explained by inhibition of the processes of oxidation caused by formic acid. This probably forms — by a reversible process — a complex compound with the iron in the respiration enzyme.

2. Acidosis follows inhibition of the processes of oxidation and is mainly due to lactic acid.

3. Amblyopia does not, as a rule, appear till acidosis has become severe, i. e. some time after the development of general symptoms.

4. If the eyes are exposed to strong light, amblyopia may precede clinical signs of acidosis.

5. Increase of metabolism favours acidosis and may thereby provoke amblyopia or aggravate it if already present.

6. A milder course is given to the poisoning if ethyl alcohol is consumed just before or, better still, just after the drinking of methyl alcohol whose oxidation is thereby checked. All signs of poisoning may be averted if ethyl alcohol is drunk repeatedly on the first few days after the drinking of methyl alcohol even though it has been consumed in large quantities.

7. The intake of much fluid may be assumed to exert a beneficial influence on the course of the poisoning.

8. A secondary diminution of vision was observed in all the cases in which normal acuity of vision was not restored. The gradual decline of the retina's functional capacity is probably due to atrophy of its blood vessels.

9. The patients who regained normal vision retained it, and they showed no morbid changes in the blood vessels.

10. The selective, destructive action of methyl alcohol on the retina is presumably due to the retina's great need of oxygen in relation to its iron content. The acidosis in itself must be assumed to play a large part in the development of this serious symptom.

11. The great variations in tolerance to methyl alcohol shown by different individuals are primarily due more to the part played by the factors mentioned under headings 4, 5, 6 and 7 in the course of the poisoning than to individual predisposition as has been commonly held.



### B. *Treatment.*

1. The acidosis should be rapidly corrected by bicarbonate whose dosage is calculated according to Van Slyke's nomogram. Treatment should begin with the intravenous injection of an isotonic (1.3 %) solution of sodium bicarbonate.

2. Liberal flushing with fluid to combat dehydration and promote profuse diuresis is indicated. Hypochloraemia is an indication for normal saline solution, and signs of inanition for an intravenous injection of a 5 per cent. solution of glucose.

3. Ethyl alcohol helps to prevent a recurrence of acidosis.

4. Gastric lavage should not be undertaken till an intravenous injection of a bicarbonate solution has been given.

5. Treatment should at first be given in a medical ward and not in an eye department.

6. The eyes require protection against light, notably during the acute stage of the poisoning, but also later on if amblyopia persists.

7. There is no reliable evidence in support of the assumption that lumbar puncture is beneficial in amblyopia.

8. Treatment with sweat baths and thyroid extract seems to be contra-indicated.

A perusal of newspaper accounts of methyl alcohol poisoning in different parts of Norway leaves one with the very definite impression that the treatment these patients receive at first is very inadequate. The rapidity with which the manifestations of the poisoning may develop, and the often lengthy journey to hospital, may explain why so many patients die on the way. Much would be gained if the doctor first summoned to the patient at once started to correct the acidosis instead of contenting himself with washing out the stomach. It is, therefore, urgently essential that every doctor should be familiar with the principles of the treatment. I hope that this preliminary study of methyl alcohol poisoning will have contributed to this end.

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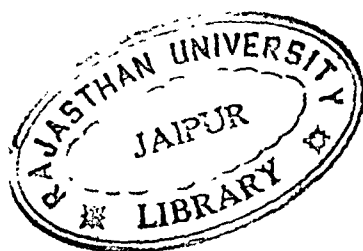
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